James Allen Heywood
"All models are wrong, but some are useful."

George Edward Pelham Box
Is Pre-competitive the right model?

What assumptions does it contain?

Other models.

• Effectiveness
• Return on Investment
• Industrial/Scale/Quality
• Science vs Engineering
Scientific Method

Ask a Question | Do Research | Form Hypothesis | Experiment | Analyze Data | Report Results

Engineering Design Process

Identify a Problem, or Opportunity | Do Research | Develop Solutions | Construct Solution | Test, Optimize Evaluate | Communicate Solution
Supply (Ideas) vs Demand (Specifications)
Industrialize and Systematize

Validation (2001)
- ALS TDI – Mouse Core
- Increased power of model

Discovery (2006)
- ALS TDI – Discovery Core
- Unbiased discovery of mechanism

Disease Models (2005)
- PatientsLikeMe
- Advanced Models of Disease
Better, Faster, Cheaper

DNA Sequencing Cost (per base pair)


0.0001
0.001
0.01
0.1
1
10
100

patientslikeme™
Small can be powerful

- Fast exchange of ideas
- Time efficient decisions
- Rapid adaptation of new information and possibilities
- Low institutional inertia and overhead
“Given my status, what is the best outcome I can hope to achieve, and how do I get there?”
Systems Model of Disease

State Variable

Force Variable
Personalized Medicine Discovery Platform

New and Developing Disease Biomarkers

Partners Novel and Repurposed Treatments
Lithium delays progression of amyotrophic lateral sclerosis

ALS is a devastating neurodegenerative disorder with no effective treatment. In the present study, we found that daily doses of lithium, leading to plasma levels ranging from 0.4 to 0.8 mEq/liter, delay disease progression in human patients affected by ALS. None of the patients treated with lithium died during the 15 months of the follow-up, and disease progression was markedly attenuated when compared with age-, disease duration-, and sex-matched control patients treated with riluzole for the same amount of time.

Results

Effects of Lithium on Disease Duration

G93A male mice were treated daily with lithium (1 mEq/kg, i.p.), starting at 75 days postnatal. The mean survival time increased from 148 ± 4.3 (n = 20, 36% of the control) to 148 ± 3.6 (n = 19, 27% of the control) and, most importantly (from a mean of 9 days to > 38 days compared with the G93A mice treated with saline).

# Significant difference from controls

* Significant difference from saline-treated mice

Graph showing ALSFRS-R scores over time for treated and control groups.
Methods - Observational study to compare those treated with lithium vs. controls

- Of those providing demographic info:
  - 3481 users
  - 3069 patients
  - 370 took lithium; 2699 control
  - 137 treated meet study criteria
  - 1368 control meet study criteria

- Employ novel algorithm to match pre-treatment disease profiles, reducing bias

- Two treatment cohorts followed:
  - Intent-to-treat [>2 mo lithium]
  - Full course [>12 mo lithium]
Distribution of Lithium Start Dates

Number of patients

Oct 07 | Jan 08 | Apr 08 | Jul 08 | Oct 08 | Jan 09 | Apr 09 | Jul 09 | Oct 09

PNAS paper published ➔

Lithium start

humberto-from-brazil
Male, 62 years
Brasilia, Distrito Federal

patientslikeme™
### Patient Information

<table>
<thead>
<tr>
<th>Patient</th>
<th>Profile Star</th>
<th>Onset Date</th>
<th>Diagnosis Date</th>
<th>Type</th>
<th>Sex</th>
<th>Age</th>
<th>Current Star</th>
<th>History Star</th>
<th># of FRS scores</th>
<th>Onset to Start</th>
<th>Start to Today</th>
<th># of data points in months before and after Lithium start</th>
</tr>
</thead>
<tbody>
<tr>
<td>humberto-from-brazil</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td>4</td>
<td>12</td>
<td>0</td>
<td>1 1 1 1 1 1 1 1 1 1</td>
</tr>
</tbody>
</table>

#### Profile

**humberto-from-brazil**
- Male, 43 years
- Onset: Arms
- On Rilutek

#### Side Effects
- Constipation
- Slurred speech
- Excessive saliva
- Weight gain or loss
- Depression
- Muscle weakness, stiffness, twitching, or tightness
- Joint or muscle pain
- Tiredness

#### Lithium Treatment
- Blood Level: 0.2 mmol/L
- Lithicarb: 150 mg/day

#### FRS
- FRS: 17

#### FVC
- FVC: 40
ALSFRS-R Scores of Patients on Lithium

Timeframe | Limit Patients to
---|---
18 months before lithium | 3 FRS points before lithium
12 months after lithium | 1 FRS points after lithium

Update Graph

Printable Version

Print a copy of this graph.
Demographics

Age at treatment start

Treated, mean = 51.3 +/- 0.8

Control, mean = 52.7 +/- 0.7

Sex

Onset site

FRS at start

Treated, mean = 33.6 +/- 0.7

Control, mean = 33.8 +/- 0.5
## Mood / Mental

<table>
<thead>
<tr>
<th></th>
<th>Severity reports — all patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None</td>
</tr>
<tr>
<td>Confusion</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td></td>
</tr>
<tr>
<td>Giddiness</td>
<td></td>
</tr>
<tr>
<td>Hallucinations (seeing things or hearing voices that do not exist)</td>
<td></td>
</tr>
<tr>
<td>Restlessness</td>
<td></td>
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</tbody>
</table>

## Mouth

<table>
<thead>
<tr>
<th></th>
<th>Severity reports — all patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None</td>
</tr>
<tr>
<td>Change in the ability to taste food</td>
<td></td>
</tr>
<tr>
<td>Dry mouth</td>
<td></td>
</tr>
<tr>
<td>Excessive saliva</td>
<td></td>
</tr>
<tr>
<td>Swollen lips</td>
<td></td>
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<tr>
<td>Tongue pain</td>
<td></td>
</tr>
</tbody>
</table>

## Eating / Appetite / Gastro-Intestinal / Urinary

<table>
<thead>
<tr>
<th></th>
<th>Severity reports — all patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None</td>
</tr>
<tr>
<td>Constipation</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
</tr>
<tr>
<td>Excessive thirst</td>
<td></td>
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<tr>
<td>Frequent urination</td>
<td></td>
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<tr>
<td>Gas</td>
<td></td>
</tr>
<tr>
<td>Indigestion</td>
<td></td>
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<tr>
<td>Loss of appetite</td>
<td></td>
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<tr>
<td>Stomach pain or bloating</td>
<td></td>
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<tr>
<td>Vomiting</td>
<td></td>
</tr>
</tbody>
</table>
Control matching

Random

Mean decline in FRS over time

Traditional

Mean decline in FRS over time

patientslikeme™
Two different disease courses

ALSFRS-R

Time
Humberto-from-brazil
Male, 42 years
Brasilia, Distrito Federal

Diagnosis
Onset: Arms
First symptom: 09/06
Diagnosis: 03/07
Genetics: Non-SOD1 ALS

ALS Condition

FRS
Progression rate percentile
- 5-10th (rapid)
- 10-25th
- 25-75th (average)
- 90-95th (slow)

FRS: 25
Latest update: 25 Dec 2007
Algorithmic matching

Mean decline in FRS over time

- Lithium (N=75)
- Control (N=75)
Kaplan-Meier estimator of survival functions

Survival [%]

Time after treatment start [mo]

- Living -- treated
- Living -- control
- Reporting data -- treated
- Reporting data -- control
James Allen Heywood