Examples of go and no-go decisions after rigorous early phase drug evaluation

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1st Example: Innovative New Pain Compound

- Small (1400 Da) stable 13-amino acid peptide
- Originally derived from cone snail venom
- Non-competitive inhibitor, through allosteric modulation, of the norepinephrine transporter
- Administered via intrathecal delivery
- Excellent potential for the treatment of intractable pain
Previous studies

• Phase I study in 20 HV, single dose i.v. administered, plasma PK and safety

• Phase I/II open-label study in cancer patients with pain, ascending doses, up to 40 mg i.t.

• Phase II study in 200 bunionectomy patients, put on hold by FDA after n=16

• Phase I study in 28 HV, single dose i.t., safety incl. EEG recordings, no CSF PK
HED of NOAEL

human equivalent doses of Xen-2174
Study design

Randomized, double-blind, placebo-controlled, serial-cohort, single ascending dose of Xen2174 or placebo PK/PD study, administered intrathecally in HV

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Xen2174 dose</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.50 mg (n=8)</td>
<td>n=3</td>
</tr>
<tr>
<td>2</td>
<td>1.00 mg (n=8)</td>
<td>n=3</td>
</tr>
<tr>
<td>3</td>
<td>2.50 mg (n=8)</td>
<td>n=2</td>
</tr>
</tbody>
</table>

**Pharmacokinetics:**
- CSF PK up to 32 hours (via intrathecal catheter)
- Plasma PK

**Pharmacodynamics:**
- Pain threshold and tolerance levels for each of a battery of nociceptive tests

**Safety**
- 24h EEG
PainCart™, a multidimensional pain test battery

- **Electrical Stimulation**  
  Olofsen and Dahan, 2005  
  Arendt-Nielsen et al., 2007

- **Pneumatic Pressure**  
  Polianskis, 2001

- **Cold Pressor**  
  Eckhardt et al. 1998 and Jones et al. 1988

- **Conditioned Pain Modulation**  
  DNIC  
  Electrical pre/post cold pressor

- **Thermal stimulation**  
  Medoc TSA-II 30Thermode  
  CHEPS

- **UVB model**

- **Thermal grill illusion**
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Results - PD

Electrical Burst PTT (mA): % change

Time (hh:mm) 0:00 12:00 24:00 36:00 48:00 60:00 72:00 84:00 96:00 108:00

-80 -40 0 40 80 120

- Placebo
- XEN0.50
- XEN1.00
- XEN2.50
Safety issues

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>Subject</th>
<th>C0 (ng/mL)</th>
<th>Cmax (ng/mL)</th>
<th>Tmax (h)</th>
<th>t½ (h)</th>
<th>AUCinf (h*ng/mL)</th>
<th>C0* Ratio</th>
<th>Cmax Ratio</th>
<th>AUC Ratio</th>
</tr>
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<tbody>
<tr>
<td>2.5</td>
<td>N</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>5.44</td>
<td>3.16</td>
<td>1.43</td>
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<tr>
<td></td>
<td>Mean</td>
<td>43700</td>
<td>33200</td>
<td>0.56</td>
<td>4.83</td>
<td>159146</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>SD</td>
<td>27400</td>
<td>16600</td>
<td>0.18</td>
<td>0.843</td>
<td>64089</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Min</td>
<td>15300</td>
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<td>59100</td>
<td>1.00</td>
<td>6.09</td>
<td>258442</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>CV%</td>
<td>62.6</td>
<td>50.1</td>
<td>31.4</td>
<td>17.4</td>
<td>40.3</td>
<td></td>
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Table 16 Noncompartmental Pharmacokinetic Parameters for Xen2174 in CSF in Human Volunteers (2.5 mg Intrathecal Bolus) with ratios with 1 mg Intrathecal bolus in dogs (*Ratios calculated from mean of male and female dogs*).

human equivalent doses of Xen-2174
“Fail early to fail cheap”

Out-of-pocket costs

Phase Transition Probabilities for All Drugs (1998-2008)

Aim: lower transition rate phase I to phase II?

From: Dickson et al. Nature Reviews Drug Discovery 2004

Source: Tufts Center for the Study of Drug Development
Question based approach
Innovative Tools for ‘Proof-of-Pharmacological-Concept’ Studies

- **NeuroCart**
  - multidimensional CNS-pharmacodynamics
  - optimized for highly frequent sampling

- **PainCart**
  - multidimensional pain test battery
  - optimized for highly frequent sampling

- **Neuroimaging**
  - PET-imaging
  - resting state fMRI
Continuous CSF-Sampling
- CNS-drug concentrations
- Aβ-, p-tau profiles, etc

Pharmacological challenge models
- proof of pharmacology for neuromodulators
- proof of pharmacology for antagonists
- disease models

PK/PD modeling
- concentration-effect relationship = proof of pharmacology
2nd example:
Partial GABA-A-Agonists for Anxiety

NeuroCart™, a multidimensional CNS test battery

- **Subjective**  
  (Bond & Lader, Bowdle)
- **Visuomotor**  
  (adaptive tracking)
- **Locomotor**  
  (body sway, finger tapping)
- **Memory**  
  (30-word learning)
- **Eye movements**  
  (smooth pursuit, saccadic)
- **Pharmaco-EEG**
- **Autonomic function**  
  (pupillometry, HR variability)
- **Neuroendocrine**
Estimation of PD-equipotent dose of full vs partial agonists in healthy volunteers
Estimation of PD-equipotent dose of full vs partial agonists in healthy volunteers

**VAS sedation**

- Δ lorazepam
- ○ TPA023 1.5 mg
- □ TPA023 0.5 mg
- ● placebo

In VAS Alertness above baseline (ln mm)

Time (minutes)
Demonstration of subtype selectivity in healthy volunteers

alpha1/alpha2 vs SPV/VAS-slope
Uncertain dose estimates by (non-selective) flumazenil PET
Confirmation of clinical efficacy
in PD-predicted dose range

Clinically Effective TPA023 Dose 1.5-4.5 mg BID

Change in HAM-A,
TPA023 vs. placebo

Week of study

1  2  3  4

PBO/Drug
60/61  48/43  45/37  36/33

***  *  *  

-5 -4 -3 -2 -1 0

Week of study

Overall conclusions

• Investing in the early phase of drug development is likely to lead to cost savings later on.

• In clinical development try to answer first the question with the highest uncertainty that is resolved at the lowest cost.

• PET does not always yield proof of BBB penetration or target engagement, while showing a concentration-CNS effect relationship does.

• Try to include PD already in the earliest clinical studies and determine concentration-effect relationships prior to phase II.

• Use multidimensional PD test batteries to profile new compounds.
Questions
Backups
Table 1
Average out-of-pocket clinical period costs for investigational compounds (in millions of 2000 dollars)\(^a\)

<table>
<thead>
<tr>
<th>Testing phase</th>
<th>Mean cost</th>
<th>Median cost</th>
<th>Standard deviation</th>
<th>N(^b)</th>
<th>Probability of entering phase (%)</th>
<th>Expected cost</th>
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</thead>
<tbody>
<tr>
<td>Phase I</td>
<td>15.2</td>
<td>13.9</td>
<td>12.8</td>
<td>66</td>
<td>100.0</td>
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<tr>
<td>Phase II</td>
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<tr>
<td>Long-term animal</td>
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<td>3.1</td>
<td>4.8</td>
<td>20</td>
<td>31.4</td>
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<tr>
<td>Total</td>
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\(^a\) All costs were deflated using the GDP Implicit Price Deflator. Weighted values were used in calculating means, medians, and standard deviations.

\(^b\) N: number of compounds with full cost data for the phase.
The rise and fall of a biotech company

Xenome is founded

Xenome Ltd is founded

Both CEO & head drug development leave Xenome

Two board members (investors) leave Xenome


$ 1.25 m investment

$ 1.25 m investment

$ 3.75 m new share issue

$ 2.5 m new funding

Ziconotide licensed by FDA for US market

Ziconotide licensed by EMA/EC for EU market


EU patent

US patent

Japan patent

$ 10 m equity finance

$ 6 m new funding

$ 6.25 m new funding

$ 5 m new funding

Pre-clinical studies on Xen2174 (in vitro, rat and dog)

Additional dog studies as requested by FDA

Phase I - Xen2174 healthy volunt. IV admin.

Phase II - Xen2174 bunionectomy patients IT admin.

Phase I/I - Xen2174 oncology patients IT admin.

Phase I - Xen2174 healthy volunt. IT admin. / pain tests & EEG

FDA/CDER IND approval for Xen2174

FDA puts phase II - Xen2174 on hold

End of Xenome Ltd
Results - PK

CSF concentration–time profiles of Xen 2174
CSF concentrations
human vs dogs

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## Out-of-pocket costs

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<th>Study phase</th>
<th>Costs</th>
<th>Details</th>
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<tbody>
<tr>
<td>preclinical</td>
<td>$ 2,000,000</td>
<td>Discovery and pharmacology</td>
</tr>
<tr>
<td>GLP preclinical</td>
<td>$ 4,500,000</td>
<td>Toxicology and PK</td>
</tr>
<tr>
<td>clinical</td>
<td>$ 10,500,000</td>
<td>Phase I study in HV: plasma PK and safety</td>
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<tr>
<td></td>
<td></td>
<td>Phase I/II study in cancer patients with pain</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Phase II study in 200 bunionectomy patients</td>
</tr>
<tr>
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<td></td>
<td>Phase I study in HV with EEG recording (no CSF PK!)</td>
</tr>
<tr>
<td></td>
<td>$ 975,000</td>
<td>Phase I PK/PD study in HV with CSF PK and pain tests</td>
</tr>
<tr>
<td>Total</td>
<td>$ 16,975,000</td>
<td></td>
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Question based approach
Concentration-effect-analyses

• In case of *intended* CNS-effect: proof of
  – BBB penetration
  – target engagement
  – pharmacology

• Better understanding of drug effects
  – hysteresis
  – acute tolerance
  – determination of E0, slope, EC50, Emax

• Optimization of phase II-design
  – determination of drug (concentration) responsive effects
  – target window between ‘desired’ and ‘undesired’ effects
  – optimization of drug doses