Can assessment of CNS target engagement help to minimize risk in early development.

Philippe Danjou, MD, PhD, Biotrial
EUFEMED May 18, 2017
Blood to Brain Barrier
fMRI, ASL

SPECT, PET

EEG, MEG

COGNITION

BEHAVIOUR

WET MARKERS IN CSF, BLOOD?
Context of early Phase studies

- Generally first in Man
- Standardized study aiming to study and define:
  - Safety
  - Pharmacokinetics
  - Tolerability and AE profile
    - Define Maximum Tolerated Dose and/or safety margin
    - Define dose-limiting AEs
  - Pharmacodynamics (piggy backed) with no statistical power
  - Dose escalation between subjects with generally 6 under active and 2 under placebo

Very safe but not zero risk
Main alternative options

1. Monitor **primary effect or target occupancy** associated with efficacy (molecular imaging):
   - Impossible for first in class or relying on animal data only
   - Human ligand availability, design and cost hurdles

2. If not feasible, use a **decisionable biomarker**, downstream the MOA
   - State of knowledge and validation hurdles

- Then add a **safety margin to go above it (4-X fold ?)** for the real life of the drug
  - registration (PK, genomic, DDI and TqT studies requiring a supratherapeutic exposure).
  - Dosing errors or overdose

Would limit probability of an off target activities
Unrealistic option

• Do all in patients, « tolerability is different »
• In fact hiding behind the fact that patients need the drug not healthy volunteers and that legal aspects would differ
• With very rare exceptions it is not the safety & tolerability which is better it is the Risk/Benefit ratio which can speak away problems
• In many cases healthy subject tolerate better and surmount better an AE or toxic or exacerbated PD (adrenolytics, hypertension, liver toxicity etc..) than older, comedicated with multiple pathologies:
  – In the BIAL accident increase over the last 30 years of the « healthy age » from 35 to 50 allowed an undiagnosed comorbidity. Younger better ? Not discussed by EMA
• Those who think « no Biomarker, no Drug » continued to do so for 15 years, not motivated by individual risk but more on the optimization of success rate;

• An innovative biotech that could not fund a PET ligand development or of a predictive wet marker and minimize costs;

• Middle of the road solutions between the usual way and an alternative way would start by a change of mindset.
Progresses? 😐

How are we sure it is useful?

We do not have the budget!

We are not sure how Management will react to this change.

• Middle of the road solutions would start by a change of mindset;
Possibly precompetitive consortia would be a way to share costs and research;

Creating an ASL reference database may also pave the way to the future in a ligand-free, paradigm-free manner.
5HTT PET occupancy at 4 weeks with 5 SSRIs

Figure 6. Striatal Serotonin Transporter (5-HTT) Occupancy in Depressed Subjects After 4 Weeks of Treatment at Minimum Therapeutic Doses of Five SSRIs.

Form Meyer et al. 2004 Am J Psychiatry
5HTTP PET occupancy at 4 weeks with 5 SSRIs

**TABLE 1. Estimated Dose (ED$_{50}$) and Plasma Concentration (EC$_{50}$) Needed to Obtain 50% Serotonin Transporter Striatal Occupancy for Five SSRIs Administered to 77 Healthy and Depressed Subjects for 4 Weeks**

<table>
<thead>
<tr>
<th>SSRI</th>
<th>ED$_{50}$ (mg/day)</th>
<th>EC$_{50}$ (µg/liter)</th>
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<tbody>
<tr>
<td>Citalopram</td>
<td>3.4</td>
<td>11.7</td>
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<tr>
<td>Fluoxetine</td>
<td>2.7</td>
<td>14.8</td>
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<td>Sertraline</td>
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<td>Paroxetine</td>
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<tr>
<td>Extended-release venlafaxine</td>
<td>5.8</td>
<td>3.4</td>
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</table>

Meyer et al. 2004 Am J Psychiatry
Example of successful brain exposure-driven development

Aprepitant is a selective NK1 antagonist

Allowed full determination of plasma -Receptor occupancy in Humans

Was useful when Phase III trials in depression came back negative

Dopamine D2 striatum occupancy at Steady-State

Conventional antipsychotics

EPS

Sulpiride* 1000-1700 mg/d
Sultopride* 20-35 mg/day

Quietapine

Clozapine

* From: Takano et al. 2006 Int J Neuropsychoparmacol
Fantastic tool but..

• Ligand development for new MOAs timely and costly;
• **10-15K€** per [radiosynthesis-dosing-acquisition-processing]
• Not easy to synchronize with a FTIM usually tuning algorythm downward from MTD which is more cost-efficient
• Coupling factors may be variable (e.g. biological clocks) and be misleading in some rare cases as sleep
• Clozapine would have been overdosed based on historical references
Arterial Spin Labeling

- Magnetisation of blood at the level of carotid arteries by RF (Hanning pulse)
- Signal moves up as tagged blood flows up as a function of CBF
- **Quantitative measure**
- Can operate in resting state or during a task
- Sample size >20
Methylphenidate vs Atomoxetine (& placebo) using ASL

From Marquand et al. Neuroimage 2012
Published data (sensitivity matrix)

- Fentanyl
- Ibuprofen (pre-, post-surgical)
- Methylphenidate vs atomoxetine
- MDMA
- Oxytocin
- Haloperidol vs Aripiprazole
- Dopaminergics in ON-OFF PD patients
- LSD
- Quietapine vs pramipexole
- Methylphenydate in children vs adults
Next Step

• Who will create a **repository or a database** large enough? KCl well advanced

• Standardization on its way (A Guideline exists)

• Artificial Intelligence classifiers

• Dose-effect relationships should be considered based on the quantitative nature of the assay

alternative to PET based on a functional response with precision and specificity
EEG oscillations

• Useful for detecting some functional effects on brain, when a signature exists (silent compounds)
• (Animal telemetry suggested before embarking on a new MOA)
• Low cost and repeatable
• Quantitative or not but often based on p-values Sample depending of the signal magnitude, requires cross-over or baseline control, in general >16

Inadequate as stopping rule in a 6+2 // group FTIM study
Synchronisation between regions Δ(1-4Hz), θ(4-8Hz), α(8-12Hz)

Synchronisation within a region β(12-30Hz), γ(30-70Hz)

Discovered by Hans Berger 1929
qEEG – Beta1 FP1: 3 formulations of alprazolam

FP1 derivation- Beta1 Relative Energy

TIME (Hours)

-0.5 0 0.5 1 1.5 2 2.5 3 3.5 4 4.5

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S

10.51 ± 0.18
# Daytime qEEG Healthy Humans Sensitivity Matrix

<table>
<thead>
<tr>
<th>System</th>
<th>Mechanism</th>
<th>δ</th>
<th>Θ</th>
<th>α</th>
<th>β</th>
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<th>System</th>
<th>Mechanism</th>
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# Rat Electrocorticogram Sensitivity Matrix (Dark Phase)

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<tr>
<th>System</th>
<th>Mechanism</th>
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<th>Θ</th>
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<th>Mechanism</th>
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*: lack of consistent effect; ▲: increase; ▼: decrease; + high magnitude
Three dose levels of a modulator of glutamate release

**Single dose (D1-D2)** - Treatment: SAM 1 mg versus pooled placebo.

- Time point: +2h, +15h, +20.5h, +26h
- Alpha 1 (%)
  - Resting
  - Vigilance Controlled
- Alpha 2 (%)
  - Resting
  - Vigilance Controlled
- Beta 1 (%)
  - Resting
  - Vigilance Controlled
- Beta 2 (%)
  - Resting
  - Vigilance Controlled

**Single dose (D1-D2)** - Treatment: SAM 3 mg versus pooled placebo.

**Single dose (D1-D2)** - Treatment: SAM 10 mg versus pooled placebo.
Other downstream biomarkers

• Sedation using cognitive tasks
  – Adequate design, cross-over
  – Adequate training to the plateau of training effect
  – Less and less compound have this limiting AE (or no more looked at e.g. biologics, oncology etc)
  – With a really careful QC
    - With a carefully defined threshold based on a ROC analysis

With two tests and an adequate sample size some decision-making is possible, if all of the above is met
Hindmarch’s hardware
Critical Flicker Fusion

SEDATIVE

NOT SEDATIVE

CFF

Hindmarch’s hardware
Combinaison CFF CRT

Pool of 50 studies conducted with Hindmarch’s methodology
Conclusions

• A decisionable biomarker (sensitive, specific and calibrated) may be a strategy to limit the exposure in Phase I:
  – During SAD if ran synchronously to SAD
  – For MAD is a step down PET study is used before it

• Even if ideal exposure for efficacy is reached some overshoot would be needed to handle variability and pharmaceutical development.

• Very few biomarkers can have the suitable properties (PET > wet markers-ASL > Pharmacodynamics)

• Costs will be profoundly impacted and a precompetitive strategy would be an option.