Difficulties in translation from animal to man: some examples from neuroscience research

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Biannual non-clinical statistics conference
September 2012, Potsdam

about this talk

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Difficulties in translation from animal to man: some examples from neuroscience research

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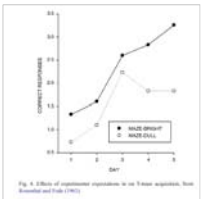
[1] AstraZeneca, [2] Eli Elly, [3]Janssen, [4] GSK; at various times the duration of the collaboration.

removing the blind



Lindner, 2007, Pharmacology and Therapeutics, vol 115, p148. *Animals trained to run in the dark for a food reward. Note the starting value on the vertical axis.*

Animal experiments are difficult. Even a verbal suggestion of an effect (that the animals are bright or dull) can, in extreme (?) cases, affect the results.

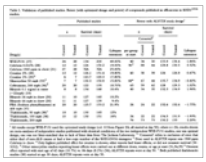
Is this a widespread effect? How often does it happen? Can we reproduce it?

Prinz et al., 2011, Nature Reviews Drug Discovery, vol 10, p712

a defining challenge for scientists and statisticians across the pharmaceutical industry

(see previous talk)

- issues with repeatability also occur in neurosciences (right) and they can be particularly difficult
- but what about translation? Are there any specific challenges to predicting from animals to man?
- this is the subject of this talk



Scott et al., 2008, Amyotrophic Lateral Sclerosis, vol 9, p4. *Quoted responses of between 20% and 40% dropped to less than 2% under retesting.*

why neurosciences?

previous examples came from neurosciences: why is this such a fertile area?

- the brain is very complicated and difficult to understand
- it is also very remote, shielded by the blood brain barrier
- many of its diseases are only partially understood
- it does complicated things in complicated ways: how do you measure cognition in animals?
- animals remain important: how could you model cognition without animals? Potentially even more difficult.

Translation is an key driver throughout the drug development process and animal models play an important part.

This talk aims to illustrate some of its challenges through some simple examples taken from neurosciences. In particular, we look at Alzheimer's disease through a European collaboration on translation from pre-clinical into man.

Alzheimer's disease (AD)

- a widespread neurodegenerative disease leading to cognitive impairment, difficulty with memory and progressive brain atrophy
- the most common form of dementia (approximately 36 million worldwide, 2010) set to rise to 115 million by 2050
- diagnosis difficult and the disease is not fully understood. No single theory but may be related to beta-amyloid plaques or tau protein tangle formation within the brain
- not clear when the disease starts. May have developed it over many years before symptoms first show
- an area of unmet medical need. No cure but some symptomatic treatments available

challenges for medical research

- many studies fail on efficacy in phase three clinical studies
- cognition is very human and difficult to mirror in animals. How do animals think?
- some lab animals (e.g. mice) don't get it at all so many models have to be *constructed*
- how predictive are animal models?

What can we do: by-pass animals altogether? More *in vitro* and *ex-vivo* experiments? Improve the basic science? Move into research in something else?

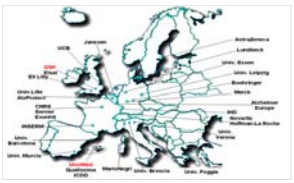
Many challenges and many options. Too much for a single organisation?

the Innovative Medicines Imitative (IMI)

- €2 billion budget from the European Union and the European Federation of Pharmaceutical Industries and Associations (EFPIA)
- **currently over 30 projects focused on a wide range of areas.**
- for each euro contributed in kind by industry, the EU matches one euro in research grants.
- projects are time limited, pre-competitive and required to share data and results publicly after completion. Formal leadership, formal controls and external review.

and PharmaCog IMI

- a consortium of 30 partners across industry and universities to improve the prediction of pre-clinical models in Alzheimer's research
- a budget of €27.7 million over 5 years. Currently half way into the project's duration
- lead partner is GSK assisted by the University of Lille



Includes dedicated work packages to support PK/PD and statistics with up to* 8 industrial statisticians to provide technical support and guidance. But what does the project actually do?

* effective FTE much less: between 1 and 2

PharmaCog objectives

"to develop and validate the models required to increase the effectiveness of the drug discovery process in Alzheimer's disease"

→ better pre-clinical models for efficacy in the clinic

↓ validated markers for disease progression and patient stratification

↘ better translation of PK/PD markers to aid dose selection

idea: address each question by matching packages of pre-clinical and clinical experiments.

aim: to develop a biomarker panel or, a 'matrix', to model the translation between pre-clinical and clinical platforms.

statistics: to ensure that the experimental design, data and analytical methods are in place to achieve this goal.

develop and validate?

what if ...

animal efficacy \ clinical efficacy	no	yes	
no	45	**4**	49
yes	13	**10**	23
	58	**14**	

you could never do this in practice

we would be happy just to see one !!!

if you can't evaluate efficacy through to a working drug ⇨ **compare through to some intermediate endpoint that may be relevant** ⇨ **a biological model: something that may look like the disease that you can measure**

(beware of the small print!)

example IMI area: challenge models

- can't test for Alzheimer's directly so create conditions associated with the disease
- apply treatment to try to reverse them
- challenges may be chemical or physical (acetylcholine inhibitors) or physical (e.g. TMS)

look for models which can be applied and tested clinically and in pre-clinical species. A non-trivial task.
Risk of face validity!

Provides a test for translation ***conditional*** on the biological model.

If the biological model is correct, agreement suggests good prediction of efficacy into clinical trials. Negative results mean when may have to look at our experimental models again.

This is a widespread idea. Transgenic animals are often engineered to express genes which we think are important for our disease. These too are biological models but make it possible to study many disease that otherwise would be impossible.

further example: equivalent responses?

- both humans and animals interact naturally with touch screens
- makes it much easier to devise tasks similar between animals and man
- and area of on-going research

Need to standardise and validate protocols. Are the studies sufficiently powered? Can we replicate them between sites? What are the best ways to analyse and compare their results?

Beware of face validity! Are different experiments actually measuring the same thing? Do animals and humans approach the same tasks in the same way with the same cognitive techniques and parts of their brain? By collecting data and understanding these experiments, we hope to better understand these questions and hence the relevance of our models of translation.

... and many more

- other experiments and platforms include:
  - EEG and MRI imaging (including effects of challenges, drugs and beta-amyloid load)
  - electrophysiology
  - healthy and MCI (potential 'pre-Alzheimer') populations
  - PK/PD modelling (a key translational framework, focus of our sister pharmacology work package)
  - cognitive and behavioural tests (e.g. picture recognition and CANTAB in man, novel object recognition and others in animals)
  - various different animal species and transgenic strains
  - specialised biochemical endpoints

Underlying questions are scientific but are motivated by a wish for a more model based approach to translation.

A strong overlap with statistics: an area to which we can contribute.

the rôle of the statistician

- **traditional support**
  - help with experiment design and analysis
  - ensure that results are repeatable and representative
  - try to raise standards of reporting and analysis across all the partners in the consortium. Scientists have a very diverse range of backgrounds and approaches. Support typically limited by resource to providing guidance rather than hands on support.
- **translational support**
  - help align experiments to quantify translation and points
  - discuss and formalise ideas motivating translation
  - ensure that all the data is in place and usable to for a multiplatform analysis *
  - develop quantitative models and methods to validate the potential of the biological models for translation into clinical studies. This was the original motivation for this collaboration!

* data management, synchronising results across 30 partners, represents a major challenge for studies of this type.

and the rôle of collaboration?

- questions to large for a single organisation
- brings together may diverse technologies and experiences
- a safe environment to exchange ideas and insights
- provides funds and direction to fundamental research
- many questions biology specific: focus on a single area
- allows us to challenge models between sites and laboratories
- professionally rewarding

conclusions

one very animal-centric view of translation

- animal models remain central but
- translation is an interesting and challenging area well suited to external collaboration
- difficult to do in a single company
- a key question if we are to be able to bring drugs to market for important and difficult diseases
- **matches the questions actually being asked by the scientists**
- a research area of unmet need?
- **an interesting area where statistics can make an active contribution**
- many of its learnings may also be translatable to other disease areas

acknowledgements

- colleagues on PharmaCog work packages 7 and 8 on slide 3 (below) and Darrel Pemberton (Janssen) for opening graph on operator bias
- scientific colleagues throughout the consortium

thank you for your attention!