

# All in the Mind

## Peter Gaskin at Aptuit Consulting assesses the failure of neuroprotectives in the clinic and questions whether the lessons can be applied to the design of animal models for other CNS indications

Animal models for CNS disorders have been shown to have limited predictive power for man, which in many cases is due to weaknesses in the animal models themselves. However, these models can often provide the information which is key to ensuring efficacy throughout formal preclinical development and Phase I clinical trials. So, how can the investigator weigh up the strengths and weaknesses of different models in order for them to be used effectively so as to ensure that efficacy seen in animal studies translates into the clinic? This article will discuss the issues in relation to stroke, where a number of promising therapies have failed in the clinic, identifies broader relevance to other CNS conditions, and considers how to ensure that animal models enhance the prediction of efficacy in patients (1).

### DEVELOPMENT OF THERAPIES FOR STROKE

Stroke is described as the rapid loss of brain function due to damage or a blockage of the blood vessels supplying blood to the brain, and can be due to a haemorrhage or ischaemia caused by thrombosis or embolism. Whilst these mechanisms all involve disruption of the blood supply to the brain, the range of mechanisms leading to disruption of blood flow and the extent of damage offers a range of potential therapeutic interventions, whilst making selection of the appropriate preclinical models more difficult (see Figures 2-4).

Since the approval of Alteplase (tPA) in acute stroke therapy in 1995, the number of neuroprotective agents for stroke in development increased rapidly. However, it became apparent that the hundreds of promising preclinical leads pushed into clinical trials were not demonstrating efficacy in those studies. High profile failures such as nimodipine, Cerestat's failure in Phase III trials in 1997 and tirilazad's failure to show efficacy in clinical trials, reflected millions of dollars of development costs and led to a lack of industry confidence in this therapeutic area (2,3). Specifically for stroke, the promise of

neuroprotectives was called into question, and whilst a few companies continue to pursue opportunities in this area, many shifted from development of neuroprotectives to drugs acting later in the ischaemic cascade with neurosurvival and remodelling strategies (4).

### GUIDELINES FOR DESIGN OF ANIMAL STUDIES

When the animal studies mentioned were being conducted, some general recommendations for good animal study design were already in place:

- Absence of bias
- High power – the investigator should conduct power calculations using well-considered assumptions in order to ensure that animal studies are sufficiently powered to reliably predict efficacy
- Wide range of applicability – so that one study design can be used for compounds with a wide range of expected responses
- Simplicity
- Amenability to statistical analysis

Simultaneously to the shift in therapeutic focus, a critical inspection of the preclinical studies which supported these products' move into development was undertaken. In many cases, this showed flaws in animal study design and a number of groups conducted an investigation into these studies, suggesting ways in

which study design could be improved in order to avoid such failures in the future. The subsequent guidelines issued following the STAIR symposium made recommendations setting out ways to improve the design of preclinical studies with neuroprotective agents for stroke and build significantly on the original general aspects proposed by Festing (5). Recommendations include:

- Drugs tested in blinded-randomised studies on rodents with models of focal cerebral infarction that permit extended recovery
- Results replicated in at least two laboratories with adequate physiological modelling
- Studies in permanent blood flow occlusion and reperfusion models

Table 1: Poor translation of efficacy in animal models to man

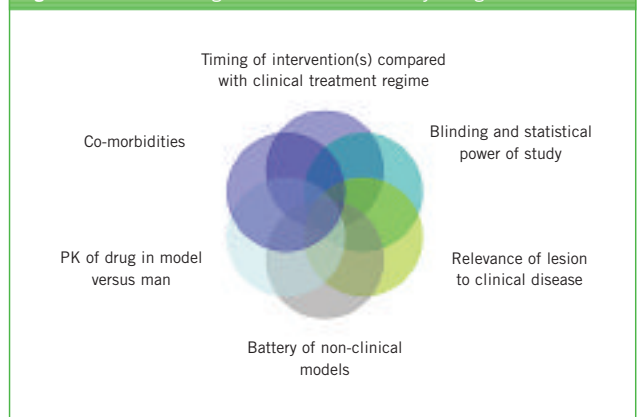
Intervention	Condition treated	Effective in animal	Effective in man	Outcome
Thrombolysis	Acute ischaemic stroke	↓ infarct volume by 24% ↑ neurobehavioural scores by 23%	✓(↓ death and dependency)	Correlation, but efficacy overstated
Tirilazad	Acute ischaemic stroke	↓ infarct volume by 29% ↑ neurobehavioural scores by 48%	✗(↑ death and dependency)	Poor prognosis of clinical efficacy (different interval between injury and treatment in animal versus man)

Table 2: Systematic review of flaws in stroke model animal study design

Intervention	Random allocation to group	Adequate concealment of allocation method	Blinded assessment of outcome
Thrombolysis	38%	20%	21%
Tirilazad	67%	6%	72%

Adapted from Perel P *et al*, 2007 (12)

Figure 1: Elements of good animal model study design



- Use of a route of drug administration that is feasible for clinical development, in order to ensure agents cross the blood-brain barrier
- Recovery of sensorimotor function of the contralateral limbs and cognitive function
- Understanding relevance of sex and age of animals
- Careful assessment of dose-response
- Time window studies conducted showing benefit at delayed timepoints after stroke onset

Since 1999, the STAIR guidelines have been the subject of much debate and have undergone further development by other researchers (7). Fisher also identified a number of problems with animal studies for acute stroke which add to the STAIR recommendations (6,8). In particular, Fisher indicated that animal models should reflect the patient group, thus not permitting the use of young animals. Moreover animal models should be reflective of the patient population and should include co-morbidities, for example hypertension. Drug treatment before induction of ischaemia or shortly thereafter does not reflect the clinical situation, and is therefore unlikely to provide an outcome which is reflective of clinical efficacy.

Despite meeting many of the key recommendations of the STAIR guidelines, (and the STAIR II guidelines for stroke clinical study design) poor translation of stroke therapies from animal models into the clinic continued as seen in the failure of Astra Zeneca's NXY-059, which 'showed no efficacy' in the pivotal SAINT II Phase III trial. Savitz and Fisher have suggested that preclinical data were not as robust as initially thought and show a lack of data replicating neuroprotective effects after three hours in the transient occlusion model and lack of a clinically relevant model of embolic stroke (10). Such failures have a real impact not only in terms of the millions of pounds of development costs, but also in share price as evidenced by the 5.75 per cent drop in Astra Zeneca's share price the morning after the announcement of the failed trial.

A number of systematic reviews continue to be performed highlighting poor study design in animal experiments for stroke including a number by the CAMARADES group (11). A recent systematic review by Perel showing the comparison of treatment

effects between animal experiments and clinical trials included two stroke treatments where there was evidence of a treatment effect (12):

- Thrombolysis using tissue plasminogen activator (tPA) or related agents in acute ischaemic stroke
- Tirilazad in acute ischemic stroke

The authors highlight limitations of animal models and best practice which they identified from their systematic review. The animal models of stroke were more aligned with results from clinical trials than those for other treatments reviewed, such as traumatic head injury, and the authors associated this with the fact that these models were more representative of the clinical condition. In particular, the stroke models more closely reflected the time between the injury and start of treatment, and also included co-morbidities such as hypertension and diabetes, making them more reflective of the patient population.

However, the details of the animal models reviewed showed that the quality of design was poor, as detailed in the percentage of studies implementing key aspects of the STAIR guideline, as well as recommendations from Festing relating to study design. It is clear that this was likely to be a contributory factor leading to poor prognosis of clinical efficacy in these cases.

Hence, there is still significant scope for improvement in the use of animal models for stroke. One should not of course consider animal experiments only. The STAIR II guidelines recommended changes which should be made to the design and conduct of clinical studies in stroke, and Ford has recently explored the

Figure 2: Stroke aetiology 1

Ischemic infarct

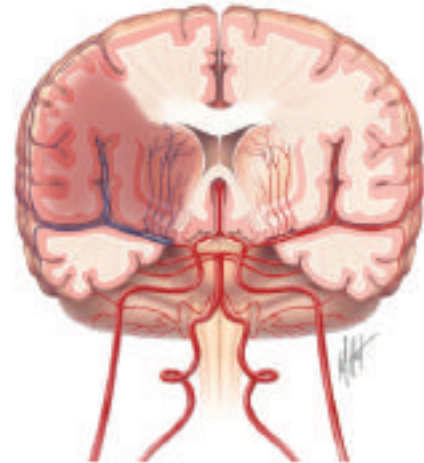


Figure 3: Stroke aetiology 2

Cerebral haemorrhage

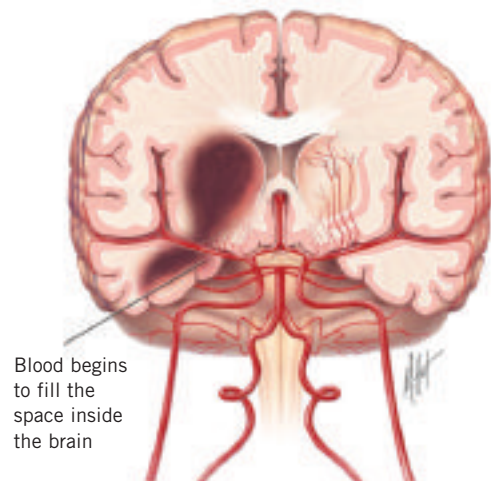
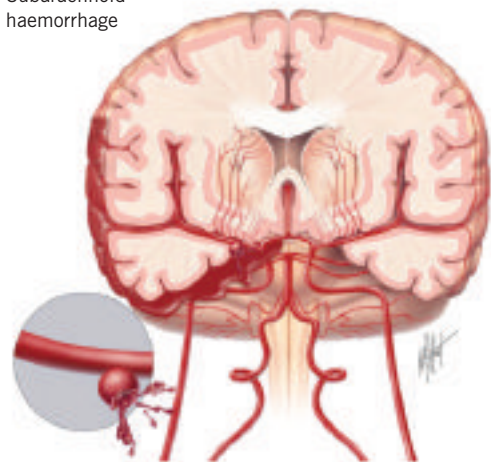


Figure 4: Stroke aetiology 3

Subarachnoid haemorrhage



interface between preclinical and clinical studies, and how surrogate markers might be used to obtain earlier indications of clinical efficacy (or the lack of) (13).

## OBJECTIVE ASSESSMENT OF ANIMAL DATA

Publication bias tends to lead to over-interpretation of the predictive value of animal models based on published scientific literature, as it does in skewing meta-analysis of clinical trials. Whether the bias relates to the publication of positive results from animal models in preference to results from animal studies using the same models that show poor predictive value, or whether it is manifested as an over-representation in publication of positive clinical trial results, the outcome is an over-statement of the predictive power of animal models.

Robust models should be developed and are used most effectively as part of a battery of *in vitro* and *in vivo* models. By communicating effectively and working closely together, the development team can familiarise themselves with each others' needs more closely, and models can be refined to more accurately reflect the clinical condition. In interpreting the data, a better understanding of the models themselves and their limitations will also limit the propensity to over-predict on the basis of results from one model. Good communication between team members will enable improvements to be made to existing animal models as new techniques and biomarkers become available. Additionally the design of clinical studies will see vast improvements in terms of where the end-points and biomarkers are selected, which can be translated effectively from preclinical efficacy studies.

## CONCLUSION

Whilst many animal models are good predictors of the efficacy of therapeutic interventions in the clinical setting, the development team is advised to:

- Understand limitations of the available animal models
- Design unbiased, statistically robust studies
- Use a battery of *in vitro* and *in vivo* models with different strengths to explore efficacy
- Develop an in-depth understanding of the mechanism of action of the drug before it is moved into clinical development

## About the author



Peter Gaskin holds BSc in Biochemistry from the University of Surrey and a PhD from the University of Nottingham, and has worked in pharmaceutical R&D for over 19 years. He began his career working in mechanistic toxicology, drug metabolism and pharmacology at ICI's central toxicology laboratory, followed by a number of posts in research and regulatory toxicology in the pharma and CRO industries. In 1999 Peter joined Quintiles, firstly as a Program Manager and subsequently as Associate Director and Head of Program Management. Following Aptuit's acquisition of Quintiles preclinical business in 2005, Peter became a Principal Consultant in the newly-formed Aptuit Consulting Inc where he advises clients on non-clinical development strategies. He is a member of the British and European Toxicology Societies and a member of TOPRA. Email: [peter.gaskin@aptuit.com](mailto:peter.gaskin@aptuit.com)

- Design studies taking key aspects of the clinical disease into account
- Use the intended clinical treatment regime in animal studies
- Understand the relationship between PK and PD in animal efficacy models
- Work closely and effectively with those conducting the animal studies as well as clinicians
- Apply knowledge of good design and model limitations in order to review the literature

Rigorous conduct of animal studies and the use of multiple models of efficacy will provide more reliable data, which gives more confidence of translation in clinical trials. The increased quality and reliability of the animal efficacy data should also provide additional assistance in the design of early clinical trials. The lessons learnt from the use of animal models of stroke detailed above have relevance to the design and conduct of animal studies in other CNS indications, and also have broader relevance to the use of animal models in drug discovery for other indications.

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