

Do stroke models model stroke?

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Stroke is one of the leading causes of death worldwide and the biggest reason for long-term disability. Basic research has formed the modern understanding of stroke pathophysiology, and has revealed important molecular, cellular and systemic mechanisms. However, despite decades of research, most translational stroke trials that aim to introduce basic research findings into clinical treatment strategies – most notably in the field of neuroprotection – have failed. Among other obstacles, poor methodological and statistical standards, negative publication bias, and incomplete preclinical testing have been proposed as ‘translational roadblocks’. In this article, we introduce the models commonly used in preclinical stroke research, discuss some of the causes of failed translational success and review potential remedies. We further introduce the concept of modeling ‘care’ of stroke patients, because current preclinical research models the disorder but does not model care or state-of-the-art clinical testing. Stringent statistical methods and controlled preclinical trials have been suggested to counteract weaknesses in preclinical research. We conclude that preclinical stroke research requires (1) appropriate modeling of the disorder, (2) appropriate modeling of the care of stroke patients and (3) an approach to preclinical testing that is similar to clinical testing, including Phase 3 randomized controlled preclinical trials as necessary additional steps before new therapies enter clinical testing.

Introduction

Cerebrovascular disease, including stroke, is the second most frequent cause of death worldwide. Stroke imposes a tremendous socioeconomic burden because the large majority of patients that survive the acute course of the disease remain physically or mentally disabled. Roughly 5 in 100 adults suffer a stroke in developed countries, and figures on stroke mortality show a high degree of variability but are generally ~50-100 per 100,000 in the Western world (Donnan et al., 2008). Although there has been a substantial decrease in stroke incidence in high-income countries, stroke incidences in low- to middle-income countries have shown an alarming increase

of more than 100% over the past decades (Feigin et al., 2009).

Pathophysiology of stroke

Ischemic stroke is a heterogeneous group of diseases, but it can be differentiated into a few clinical entities: transient or permanent embolic or thrombotic occlusion of a cerebral artery leading to a substantial reduction of blood flow in the territory of this artery causing focal cerebral ischemia. The modern understanding of stroke pathophysiology extends beyond the immediate effects of impaired local blood flow. The principal mechanisms, including complex cellular and molecular cascades, are well established and have been reviewed in detail elsewhere

(Dirnagl et al., 1999; Mergenthaler et al., 2004; Moskowitz et al., 2010).

The events that take place in the ischemic core and the surrounding area (the so-called penumbra) follow a stereotypical spatiotemporal pattern. The immediate mechanisms of damage include excitotoxicity, peri-infarct depolarizations, the production of reactive oxygen and nitrogen species, and tissue acidosis. Later on, inflammation and programmed cell death (apoptosis) also contribute to brain tissue damage. In parallel with these destructive cascades, endogenous mechanisms of protection, regeneration, (vascular) remodeling and repair – ultimately leading to amelioration of brain damage – as well as the damaging and regenerative potential of post-stroke inflammation, have been recognized (Dirnagl et al., 2009; Mergenthaler and Dirnagl, 2011; Moskowitz et al., 2010).

Drawbacks in translational stroke research

Despite tremendous research efforts by basic and clinical scientists, to date the only effective therapeutic measures are early revascularization [mostly by systemic thrombolysis using recombinant tissue plasminogen activator (rtPA)] and supportive care aimed at reducing acute complications (stroke unit concept, craniectomy) (Donnan et al., 2008). Moreover, despite an overwhelming experimental literature demonstrating substantial therapeutic success, the translation of basic research findings has led to devastating results in many clinical trials (Dirnagl and Fisher, 2012).

It is therefore timely to ask how well our stroke models model stroke and whether they are geared towards answering clinical questions. Do we need to consider weaknesses in our interpretation of the pathophysiological cascades? It might be that (1) these cascades are wrong or meaningless for human pathophysiology; (2) the targets that were identified might not be effective for

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Clinical and basic research opportunities

- Improve modeling of disease (e.g. focal transient or permanent focal ischemia of a large vessel territory; white matter stroke)
- Improve modeling of the stroke population (using aged, multi-morbid animals)
- Introduce modeling 'care' of stroke patients (incorporating concepts such as stroke units, treatment of comorbidities and rehabilitation)
- Introduce modeling of clinical trials (e.g. randomization, placebo controlled, blinded, large groups, multicenter, and define inclusion and exclusion criteria).

therapeutic targeting in humans, in whom we aim to improve long-term outcome; or (3) complex pathophysiological cascades are redundant, and targeting of just one cascade or mechanism might not be effective to treat stroke in humans.

Yet, there is good experimental and clinical evidence that the basic pathophysiological concepts of stroke are well reflected by our common models, although stroke patient populations are typically more complex than animal populations in standard stroke models. The concept of the ischemic penumbra, which established that infarction grows from the core ischemic lesion to the surrounding and potentially salvageable tissue, is a good example of how basic research findings have effectively translated into clinically relevant pathophysiological concepts (Astrup et al., 1977; Heiss, 2011). Likewise, the concept of stroke-induced immunodepression causing post-stroke infections demonstrates that stroke not only affects the brain, but also the entire body (Chamorro et al., 2012; Meisel et al., 2005; Prass et al., 2003).

In this Clinical Puzzle article, we discuss the advantages and limitations of common stroke models. Although these models effectively model the disorder (i.e. they are useful for dissecting mechanisms of stroke pathophysiology), they are not well suited for modeling the treatment and care of stroke patients (i.e. translating research findings into therapeutic concepts), who suffer not only from an acute but also a chronic phase of the disease. We therefore introduce the concept of modeling care of stroke patients in preclinical stroke models.

Stroke research: lost in translation?

Research on stroke over the last decades has revealed many potential therapeutic targets, mechanisms and neuroprotective strategies (Iadecola and Anrather, 2011; Macrez et al., 2011; Mergenthaler and Dirnagl, 2011; Mergenthaler et al., 2004; O'Collins et al., 2006; Vosler and Chen, 2009). However, the

lack of substantial innovation beyond well-established therapeutic strategies (i.e. early reperfusion, usually by intravenous thrombolysis with rtPA, and supportive care on dedicated stroke units) indicates a 'translational roadblock' (Endres et al., 2008).

Several attempts to identify and overcome this roadblock have been made in recent years. Among other challenges, heterogeneity in stroke pathophysiology (Endres et al., 2008), weaknesses in animal models of stroke (van der Worp et al., 2005), poor methodological and statistical standards (Crossley et al., 2008; Dirnagl and Macleod, 2009; van der Worp et al., 2010a), negative publication bias (Sena et al., 2010), and incomplete preclinical testing (Dirnagl and Fisher, 2012; Philip et al., 2009) all have been identified as potential obstacles. However, poor study design and inadequate statistical analysis are problems not restricted to preclinical stroke research; rather, these are problems that are common to preclinical as well as clinical research in many areas (Bath et al., 2007; Bath et al., 2012; Crossley et al., 2008; Hackam and Redelmeier, 2006; Hampton, 2002; Ioannidis, 2005; Prinz et al., 2011; Rothwell, 2005; van der Worp et al., 2010a) and have been discussed intensively for decades (Atkins, 1966; Gifford and Feinstein, 1969).

Methodology of preclinical stroke trials

The methodology of clinical trials (Begg et al., 1996) has been refined over decades (Brunoni et al., 2010; Hackam and Redelmeier, 2006; Meldrum, 2000) into today's gold standard of multicenter double-blinded randomized placebo-controlled trials. By comparison, preclinical stroke trials are in their infancy. Thus, improving the validity of translational stroke research will require following fundamental principles that are valid for most if not all areas of research. Some of these principles are outlined in the ARRIVE guidelines (Kilkenny et al., 2010), and might also include standardized

protocols and experimental or trial designs that are similar to established procedures in clinical trials (Bath et al., 2009; Begg et al., 1996; Dirnagl and Members of the MCAO-SOP Group, 2012; Macleod et al., 2009) (FDA Clinical Trials Guidance Documents, <http://www.fda.gov/RegulatoryInformation/Guidances/ucm122046.htm>, May 30, 2012).

It seems clear that proper experimental design and possibly more refined statistical analyses should be promoted. Based on systematic meta-analyses from clinical patient-based research, systematic reviews or meta-analyses of animal studies have recently been heralded as tools to improve translational success (Bath and Gray, 2009; Dirnagl and Macleod, 2009). However, the suitability of systematic reviews of preclinical research has also been questioned (Lemon and Dunnett, 2005). Indeed, it has yet to be proven that this type of analysis provides the data needed to design more successful clinical trials. As an example, a systematic review of the experimental stroke literature found therapeutic hypothermia as an effective therapy for stroke (van der Worp et al., 2010b; van der Worp et al., 2007). As such, the recently launched EuroHYP-1 trial, which tests hypothermia as a treatment for improved outcome after stroke, might provide further insight into how well systematic reviews of experimental data can predict the outcome of clinical trials. In contrast, the recent AXIS-2 trial, which tested granulocyte-colony stimulating factor (G-CSF) to treat acute ischemic stroke, was unsuccessfully concluded after clinical Phase 2 trials (Dirnagl and Fisher, 2012), despite optimistic conclusions of a systematic review of the corresponding preclinical data (England et al., 2009) and successful completion of a clinical Phase 1 trial (Schäbitz et al., 2010).

It has recently been proposed that both combination trials in experimental stroke models (O'Collins et al., 2012) and preclinical multicenter randomized controlled animal trials (Bath et al., 2009; Dirnagl and Fisher, 2012) offer additional strategies to refine and improve the translational process in stroke research. It is expected that current research protocols already resemble Phase 1 and to some extent Phase 2 trials (Bath et al., 2009; Dirnagl and Fisher, 2012). However, several novel stroke therapeutics that did not demonstrate a favorable outcome after Phase 3 clinical trials [e.g. the free-radical spin-trap drug NXY-059 (SAINT trials) or the

thrombolytic agent desmoteplase (DIAS trials)] had promising Phase 2 data (Liebeskind, 2009; Savitz and Fisher, 2007).

Emulating clinical trials at the preclinical stage

Preclinical Phase 3 trials aimed at determining therapeutic effects in heterogeneous animal populations might provide important information for subsequent clinical trials. Ideally, a randomized controlled trial format in preclinical research would essentially adapt established concepts from clinical trials and model preclinical studies according to this format, and include all core concepts of sound clinical trial design (Begg et al., 1996) (FDA Clinical Trials Guidance Documents, <http://www.fda.gov/RegulatoryInformation/Guidances/ucm122046.htm>, May 30, 2012). This includes having a steering committee

that defines inclusion and exclusion criteria, randomization, blinding, placebo control, central monitoring and data management, as well as a data safety and monitoring board managed by a preclinical research organization (pCRO). However, rather than performing different experiments in different laboratories, a format where all participating institutions follow the same (standardized) protocols (i.e. perform the intervention to test) would more closely resemble the concept of a multicenter randomized controlled trial in clinical research (Fig. 1). Therefore, such a concept would be an additional step in the 'translational pipeline' and would establish a new field of research: randomized controlled PREclinical trials according to all phases of clinical trials, including Phase 3. In addition, such a multicenter approach in preclinical stroke research might circumvent the problem of poor reproducibility in highly standardized animal experiments by introducing the systematic variation that is immanent to a multicenter trial (Richter et al., 2010; Richter et al., 2011).

Furthermore, testing combination therapy (O'Collins et al., 2012), in which different experimental stroke treatments are combined to increase efficacy, might be another way to bring experimental research closer to the clinical situation. Introducing this concept at the preclinical stage acknowledges that patients suffering from stroke are typically multi-morbid and receive multiple treatments.

These approaches offer intriguing possibilities to improve the current state of stroke research and represent a paradigm shift in the way that preclinical research is currently performed. However, they should not replace the way research to investigate mechanisms is conducted. Eventually, they need to evolve into a separate field of research that brings together multiple investigators, institutions, and regulatory and possibly funding agencies, as well as pharmaceutical companies (Bath et al., 2009). Finally, it has also been implied that clinical stroke trials are not selective enough with respect to their enrolment criteria, and thereby might miss potentially useful interventions, whereas experimental trials typically study a specific mechanism or a very specific type of stroke, and therefore yield more selective and more promising results (Gladstone et al., 2002). Thus, in that regard, clinical stroke research should also learn

from preclinical studies (Savitz and Fisher, 2007).

Common animal models of stroke

The most common animals for stroke research are rodents, mainly mice, rats and gerbils, but experimental approaches in larger animals such as cats, dogs, pigs and non-human primates also exist (Table 1). Detailed protocols as well as reviews of the advantages and disadvantages of using these models to model human stroke are available elsewhere (Braeuningner et al., 2012; Carmichael, 2005; Dirnagl, 2010; Engel et al., 2011; Fukuda and del Zoppo, 2003; Howells et al., 2010; Macrae, 2011; Mergenthaler et al., 2004; Orset et al., 2007; Sozmen et al., 2012).

Briefly, the best correlates of the clinical condition of ischemic stroke are models in which focal cerebral ischemia is induced. Models of both permanent and transient (i.e. with restoration of blood flow) focal ischemia exist. Typically, vessel occlusion is achieved by using a small intraluminal filament, a small hook or pro-thrombotic agents (see Carmichael, 2005; Dirnagl, 2010; Sozmen et al., 2012). Transient vessel occlusion takes into account the effects of spontaneous reperfusion, or the clinically more relevant situation of successful lysis therapy using rtPA. Stroke-prone spontaneously hypertensive rats exhibit pathophysiological similarities to human stroke and are among the only models currently available that are not based on an invasive procedure to induce ischemia (Bailey et al., 2011; Howells et al., 2010; Yamori et al., 1976). Thus, appropriate sham controls (e.g. intervention and immediately reversed vessel occlusion) have to be used in all other cases.

What is a good animal model of stroke?

As outlined earlier, it is clear that there is no ideal animal model of human stroke, and that the current design of preclinical experimental stroke studies offers substantial room for improvement. Considering the complex characteristics of animal models of stroke is essential when selecting an appropriate model for preclinical studies. Three aspects that are not often considered in preclinical studies are (1) the heterogeneous nature of the disease, (2) the presence of comorbidities and (3) appropriate outcome measures.

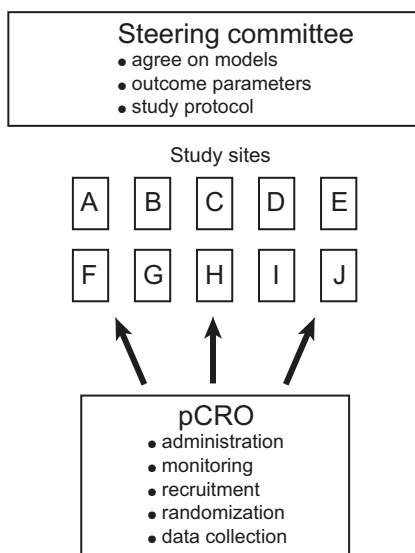


Fig. 1. Based on randomized controlled clinical trials, the final stage of preclinical testing should be to conduct a randomized controlled preclinical trial. In this scenario, a steering committee agrees on the intervention to be tested and all related aspects (e.g. models, outcome parameters, etc.). All administrative matters are centrally organized by a preclinical research organization (pCRO) and include objective criteria for the recruitment of study sites, the modes of randomization, collection of the data from the study sites and central monitoring of all aspects of the trial. Ideally, all study sites are capable of performing the same experiments (i.e. they have access to the same models and equipment). All aspects of the randomized controlled preclinical trial are monitored by an independent organization.

Modeling the heterogeneous nature of stroke

Although it might not be the sole reason for failed translational success and the negative outcome of most clinical trials in the stroke field, the heterogeneous nature of the condition has undoubtedly made treatment development a challenge. As noted earlier, many clinical trials are geared towards testing a pharmacological agent or a therapeutic strategy against outcome after stroke in general, rather than defining distinct patient subgroups (Endres et al., 2008). The heterogeneity of stroke is reflected by the wide variety of different models that have been established (Howells et al., 2010). Notably, most animals, including rodents and large animals, exhibit a similarly high degree of heterogeneity in the cerebral

vasculature (e.g. circle of Willis, collateralization) as humans do (Ashwini et al., 2008; Howells et al., 2010). Even inbred rodent strains, such as the mouse C57BL/6 strain (Beckmann, 2000; McColl et al., 2004) and different rat strains or gerbils (Howells et al., 2010), display a large degree of variability of the anatomy of their cerebral vasculature, affecting their susceptibility to stroke (Barone et al., 1993). Thus, inter-strain variability and inter-species variability might resemble variability in human anatomy to some extent (Howells et al., 2010).

Modeling stroke comorbidities

Second, most investigators disregard the fact that most stroke patients are not young or middle-aged males without any comorbidities (Howells et al., 2010; Sena et

al., 2010). However, it is these types of animals that are used in experimental stroke studies. Ideally, preclinical studies for stroke should use animal populations of mixed sex, advanced age and with various comorbidities, such as diabetes mellitus, hyperlipidemia, hypertension or obesity, in order to model the human etiology more closely. Many of these models are readily available (Howells et al., 2010). These experimental populations should be increasingly complex as a therapeutic intervention advances in the translational pipeline (Fig. 2).

Modeling relevant outcome measures

Third, it is imperative that experimental stroke studies follow more than one outcome

Table 1. Overview of common animal models of stroke

| Model | Suitable species | Advantages | Limitations | References |
|---|--|--|---|---|
| MCAO, clips, hooks, other mechanical devices | Rodents, large animals (including non-human primates) | Can also be used in larger animals | Requires craniectomy and anesthesia; technically challenging | Dirnagl, 2010; Fukuda and del Zoppo, 2003; Macrae, 2011 |
| MCAO, intraluminal filament | Rodents | Highly reproducible infarct sizes; timing of occlusion determines extent and localization of ischemic lesion; transient and permanent occlusion possible | Reproducibility depends on surgical skills; risk of hemorrhage; high mortality with large infarcts; not suitable for studying thrombolysis; infarct sizes dependent on collateralization and/or circle of Willis; requires anesthesia and surgery | Braeuninger et al., 2012; Carmichael, 2005; Dirnagl, 2010; Engel et al., 2011; Howells et al., 2010; Macrae, 2011 |
| MCAO, photothrombosis | Rodents | Very reproducible; low mortality | Requires injection of photochemical dye; early vasogenic edema | Howells et al., 2010; Macrae, 2011 |
| MCAO, thromboembolic occlusion | Mostly rodents, models in larger animals (including non-human primates) also available | Close correlation to human stroke; suitable for studying thrombolysis | Location and duration of ischemia are hard to control; requires anesthesia | Macrae, 2011 |
| MCAO, thrombin injection | Rodents | Reproducible infarcts possible | Craniectomy and anesthesia required; small infarct sizes | Macrae, 2011; Orset et al., 2007 |
| MCAO, vasoconstrictor (endothelin) | Mostly rodents, non-human primate models also available | Very reproducible; can be modified to be performed without anesthesia | Most common approaches require craniectomy; variability in potency of vasoconstrictor; variable duration of occlusion; nonspecific effects on brain | Dirnagl, 2010; Howells et al., 2010; Macrae, 2011 |
| Spontaneously hypertensive rats or stroke-prone spontaneously hypertensive rats | Rat model (developed by selective breeding) | Rats develop hypertension without intervention; mostly cortical lesions, but also mixed gray/white matter lesions | Complex phenotype (central nervous system, vasculature, immune system); brain abnormalities not only related to hypertension | Bailey et al., 2011; Howells et al., 2010; Sozmen et al., 2012; Yamori et al., 1976 |
| White matter strokes (different techniques available) | Mostly rodents, non-human primate models also possible | Important subtype of human strokes; focal and global models available; models axonal damage, myelin disruption and local astro-glial activation | Molecular and cellular pathophysiological cascades and experimental protocols not as well established as for gray matter strokes; suitability of available models highly dependent on animal used | Sozmen et al., 2012 |
| Large animal models (including non-human primates); use different techniques to occlude vessels | Different species (cats, dogs, pigs, non-human primates); different models available | Anatomy of brain and vasculature closer to human anatomy (e.g. gyrencephalic brains, substantial white matter, etc.); models with comorbidities also available (e.g. hypertension) | Requires surgical approaches; no genetic models; ethical limitations; limited use due to animal protection laws; very high cost | Fukuda and del Zoppo, 2003; Macrae, 2011; Sozmen et al., 2012 |

MCAO, middle cerebral artery occlusion. See references for further details.

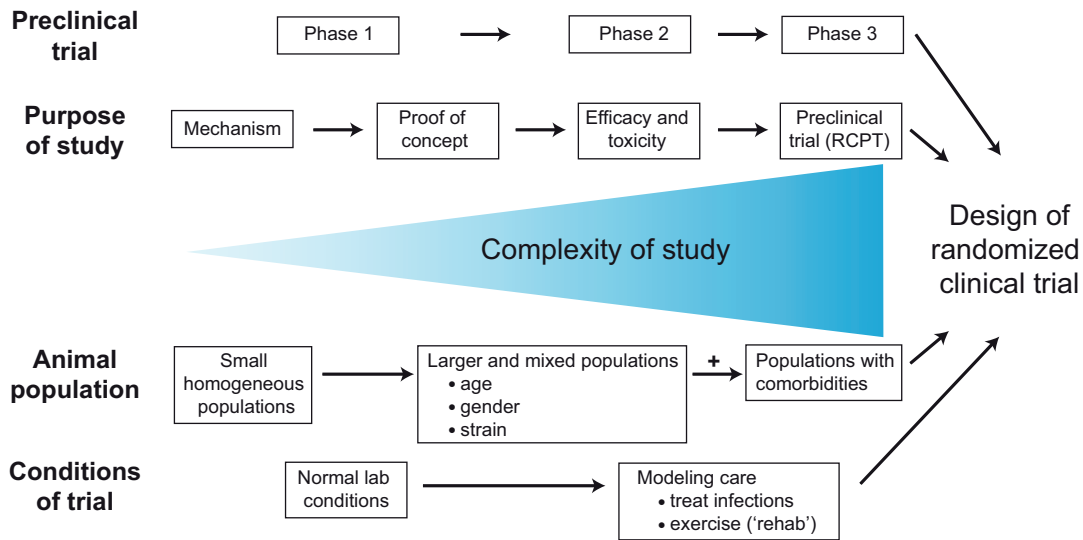


Fig. 2. The preclinical trial phases of translational stroke research. As therapeutic agents or concepts advance in development, the experimental setting increases in complexity. It ranges from small cohorts to investigate novel (pathophysiological) mechanisms to large mixed populations with (multiple) comorbidities and additional modeling of stroke care. The final stage of preclinical development is to conduct a randomized controlled preclinical trial (RCPT), ideally in a stroke unit setting. Randomized clinical trials commence after this process has been completed, and are based on evidence gained in preclinical testing.

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measure. Typically, many experimental stroke studies only report decreased infarct sizes (albeit with a tremendous effect of the studied intervention) or short-term outcome measures. However, “human strokes are mostly small in size” (Carmichael, 2005) and, ultimately, the most important outcome parameters of any intervention in human stroke are long-term (3-month) survival and functional recovery, as measured by the modified Rankin scale or Barthel index, which represent the ability of a patient to perform activities of daily life or the ability to communicate (Lees et al., 2012; Schellinger et al., 2012). Thus, similar to clinical trials, long-term survival should be used as an important outcome measure in experimental studies. Beyond comparing infarct sizes, analyses geared at investigating (long-term) functional outcome (Gladstone et al., 2002), including analysis of complex motor functions such as gait (Hetze et al., 2012), or complex long-term behavioral analysis (DeVries et al., 2001; Whishaw et al., 2008), would dramatically improve many experimental studies.

In summary, preclinical trials for the development of novel therapies for stroke should include large and complex cohorts of animals and include sex-mixed, aged animals from different strains, ideally with different comorbidities. Furthermore, complex long-

term outcome analyses should be performed to evaluate the success of a novel therapeutic concept or pharmacological agent (Fig. 2).

Modeling care of stroke patients

As discussed above, there is good evidence that currently available stroke models effectively model the disorder ‘stroke’ as well as its consequences. However, how we can model the care of stroke patients is rarely discussed.

Modeling stroke unit care

Our most successful therapeutic strategies rely on ‘intensified care’ of stroke patients in the acute phase of the disease on dedicated and highly specialized stroke units (Donnan et al., 2008). Acute care on stroke units is complex and is committed to optimizing physiological parameters such as body temperature, blood pressure, oxygenation and blood glucose levels. Furthermore, secondary stroke prevention by treating risk factors is started early. Likewise, prevention and treatment of medical and neurological complications to improve patient outcome receives equal attention.

Preventing infections after stroke

Among others, a frequent complication treated in stroke units is infection. Although infections have a detrimental effect on stroke outcome (Westendorp et al., 2011), they have

largely been neglected in preclinical stroke research (Meisel and Meisel, 2011; Meisel et al., 2005). Based on mechanistic basic research, it is now clinically and experimentally well established that stroke induces immunodepression through complex mechanisms, contributing to these post-stroke infections (Chamorro et al., 2012; Chamorro et al., 2007; Harms et al., 2008; McColl et al., 2009; Meisel et al., 2005; Prass et al., 2003).

Preventive antibacterial treatment not only prevents infections, but also improves survival and neurological outcome after experimental stroke, compared with placebo treatment (Meisel et al., 2004). Recent Phase 2b trials have successfully proven this concept (Chamorro et al., 2005; Harms et al., 2008; Schwarz et al., 2008), demonstrating that prevention of infection is effective in stroke patients (van de Beek et al., 2009). The ongoing Phase 3 preventive antibiotics in stroke study (PASS), comprising 3200 patients, is investigating whether preventive antibiotic treatment improves long-term outcome after stroke (Nederkoorn et al., 2011).

Based on our recent experimental findings with complex modeling of acute stroke care (Susann Hetze, Odilo Engel, Christine Roemer, Susanne Mueller, Christian Meisel and A.M., unpublished data), we speculate that the PASS trial will demonstrate that preventive anti-infective treatment improves

neurological outcome but not survival. As mentioned above, we demonstrated that preventive antibiotic treatment reduces mortality and improves neurological outcome compared with no treatment of infections (Meisel et al., 2004). This approach, however, does not reflect the clinical setting. Thus, in our current experimental approach (S. Hetze, O. Engel, C. Roemer, S. Mueller, C. Meisel and A.M., unpublished data), we investigated whether preventive antibiotic therapy is superior to the current clinical 'gold standard' for treating post-stroke infections. This new approach is modeled according to the current stroke guidelines, recommending early antibiotic treatment after diagnosis of infections. Preventive antibiotic treatment improved the survival after stroke compared with no treatment (placebo) but not compared with standard antibiotic treatment. However, preventive antibiotic treatment improved long-term outcome compared with both placebo and standard treatment (S. Hetze, O. Engel, C. Roemer, S. Mueller, C. Meisel and A.M., unpublished data). This example has further implications: for example, when testing treatment strategies or potential drugs, it is mandatory to consider that, even in our stroke models, we have medical complications such as post-stroke infections, which have a negative effect on clinical outcome (Engel and Meisel, 2010).

Modeling stroke rehabilitation

In the subacute and chronic phase of stroke, patients with disabilities receive highly specialized rehabilitation care. Despite evidence that such specialized treatments are beneficial (Dobkin, 2008; Gladstone et al., 2002; Hosp and Luft, 2011; Klein et al., 2012), the complexity of long-term stroke therapy is not considered in experimental or preclinical stroke studies. A recent example of complex modeling in neurological long-term rehabilitation is the successful restoration of voluntary control over locomotion after paralyzing spinal cord injury in rats using an electrochemical neuroprosthesis and a robotic postural interface (van den Brand et al., 2012).

In summary, if we are to aim for a true paradigm shift in stroke research, introducing the concept of preclinical stroke units, as well as neurological rehabilitation, should be part of the strategy. We can thus aim to more closely model stroke care and

Case study

A 47-year old male was admitted to the emergency department, complaining of a hemiparesis and complete global aphasia [NIH stroke scale (NIHSS) 14]. The symptoms had manifested suddenly 45 minutes prior to admission. The diagnosis of stroke was suspected and CT scan of the brain was performed 12 minutes after admission, excluding a hemorrhage. Early signs of cerebral infarctions were absent. Thus, the patient had no contraindications for lysis treatment and was in the appropriate time window of 4.5 hours after stroke onset. Intravenous lysis with rtPA was started 27 minutes after the patient was admitted. Thereafter, the patient was further treated on the stroke unit. Upon lysis treatment, the neurological deficit only partially improved (NIHSS 12). His past medical history was unremarkable. The cause of the stroke was a hitherto unknown atrial fibrillation. At 3 days after stroke onset, he developed pneumonia, which required antibiotic treatment and mechanical ventilation as well as further treatment on a neurological intensive care unit. Weaning was successful 6 days later and the patient was able to breathe without respirator support. Because the neurological deficit had severely deteriorated with the medical complications (NIHSS 18; Barthel index 0), the patient was referred to neurological rehabilitation 11 days after stroke onset. In the neurological rehabilitation department, he was admitted to an intensified training program consisting of physio- and occupational therapy, logopedics, and neuropsychological counseling. The patient further suffered from post-stroke depression and was treated with a selective serotonin reuptake inhibitor (SSRI). The patient recovered well: 8 weeks later, he was only moderately disabled (NIHSS 6; Barthel index 75) and was discharged to outpatient care. Transient home care was organized. Treatment was continued in a dedicated stroke outpatient clinic for 6 months. The remaining motor aphasia required further logopedic treatment; the spastic paresis of the right arm was treated with physiotherapy and intramuscular injections of botulinum toxin every 3 months. He received counseling in all issues of stroke care. At 9 months after stroke onset, the patient only had minor paresis of the right arm (NIHSS 1; Barthel index 100). Social reintegration was finally successful and the patient was able to work in his former job.

real-life treatment strategies. Therefore, we advocate the concept that 'stroke care' (i.e. complex therapeutic interventions not limited to the treatment of infections) should be implemented in future preclinical stroke studies.

Outlook

In the last few decades, most translational efforts in stroke research have failed. However, basic stroke research has contributed and continues to contribute invaluable insight into disease mechanisms and the molecular, cellular and systemic pathophysiology of stroke through a variety of different animal models. Nevertheless, many questions remain unsolved and warrant more refined research strategies.

Although currently available animal models are geared to effectively model the disease, more complex models might be needed to improve the translational success in experimental stroke research. Future strategies will implement experiences and information gained from the conduct of randomized clinical trials and from systematic reviews of published trials, include more heterogeneous animal populations (i.e. exhibiting comorbidities, variations in age, gender, strain, etc.), and will also consider modeling successful clinical concepts.

However, care should be taken not to simply replace current research concepts

that are geared towards investigating basic mechanisms. There will be no 'one-size-fits-all' approach, and some of the approaches discussed above will be difficult or even impossible to implement into basic research for various reasons. Standardized approaches that are required for translational preclinical stroke trials might even hinder the basic investigation of unidentified mechanisms. Preclinical translational trials should therefore be established as an independent novel field of research bridging mechanistic research and clinical research. Thus, rather than being discouraged from the failures of the past, we should look ahead and work together to improve the current state of translational stroke research.

COMPETING INTERESTS

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