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Title: Chase: in dogged pursuit of a therapy for spinal cord injury

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New therapies for human spinal cord injuries are badly needed (Ahuja *et al.*, 2017). It is a challenging task because injuries are heterogeneous in terms of spinal location and severity. Ideally a therapy will work for survivors with acute injuries or chronic injuries that have happened less recently. In this issue of *Brain*, Nick Jeffery and his team describe a successful clinical trial of a drug therapy for chronic spinal cord injury (Hu *et al.*, 2018) which led to an improvement in limb co-ordination during walking.

This clinical trial was carried out using dogs that had suffered naturally occurring spinal cord injuries; for example, as a consequence of road traffic accidents or herniated intervertebral discs, which occur commonly in Dachshunds and other dogs with disproportionately long vertebral columns. These injuries vary in terms of spinal level, severity and time since injury; as such, these dogs provide an opportunity to evaluate a therapy in a heterogeneous population of subjects prior to evaluating a therapy in a cohort of humans with spinal cord injuries that are likely to be heterogeneous even after selection for inclusion (Figure 1). These canine injuries have good face validity; they result from a variety of accidents rather than from controlled, defined injuries induced surgically under anaesthesia (like human injuries and unlike most other preclinical studies): accordingly, they are likely to have good predictive validity.

The candidate therapy assessed was chondroitinase ABC (“Chase”) which is a bacterial enzyme that removes sugar side chains from extracellular matrix molecules including chondroitin sulphate proteoglycans. These are found within the intact and injured nervous system and are potent inhibitors of axonal growth. Degradation of chondroitin sulphate sugar side chains with Chase has been shown to improve axon growth in vitro and in vivo in many publications in many species including mice, rats, cats, squirrel monkeys (Moon *et al.*, 2001; Bradbury *et al.*, 2002; Jefferson *et al.*, 2011; Bowes *et al.*, 2012) and now dogs. After spinal cord injury, Chase has also been shown to enhance neuroplasticity in different spinal networks leading to functional improvements in breathing (Alilain *et al.*, 2011) as well as walking (Bradbury *et al.*, 2002) and grasping (Garcia-Alias *et al.*, 2009). The fact that many independent laboratories have each found benefits of Chase with few, if any, reports of side effects, is encouraging.

This clinical trial is of an unusually high methodological standard for work using animals. It is a properly controlled, randomized, clinical trial with observers blinded to intervention. The treatment was delivered using clinically-feasible percutaneous injections into spinal cord under fluoroscopic guidance; control dogs received needle puncture of the skin to maintain blinding of observers. Relatively large volumes were injected directly into the spinal cord parenchyma and in the future it will be important to fully evaluate the risk factors and safety of this approach. The trial was based on prior sample size calculations (with power of $\geq 80\%$ to detect the effect size of interest) and a large number of dogs (60) were randomised into the trial. The primary outcome measure was analysed on an Intention-To-Treat basis (i.e., involving all animals that were randomized to treatment); to enable this, statistical analyses involved a multilevel linear model which can handle missing data. Since the subjects were pet dogs, their tissues were, quite understandably, not available for anatomical, molecular and biochemical assessment of mechanism of recovery although neurophysiology was used to seek changes in connectivity. There were no differences between groups in improvement in bladder compliance. Adverse events were minor and there was no evidence for increased limb withdrawal responses in response to Von Frey filaments. Although it is stated in the paper that the primary outcome measure was pre-specified in a grant application, in the future it will be even better if veterinary clinical and preclinical trials of this kind are pre-specified publically in a date-stamped immutable repository (e.g., in a Registered Report; <https://cos.io/rr/>).

The magnitude of the improvements in co-ordination in this paper may be modest if one looks at the average difference between the groups but several Chase-treated dogs (3 out of 30, reflecting 10% of the treated population) recovered independent ambulation. Moreover, this effect size is likely to be a reasonable estimate of the “true” population effect size because this is a study involving a reasonably large number of dogs which is of very high methodological quality. Furthermore, given that Chase induced recovery in dogs treated many months after spinal cord injury (i.e., after the phase of cell death is largely complete), it is encouraging that, additionally, Chase can increase recovery after acute spinal cord injury via neuroprotective mechanisms (Bartus *et al.*, 2014); accordingly, the magnitude of improvements in larger animals might yet be increased if the intervention can be given earlier after injury.

Furthermore, continued efforts to optimise this therapy are being made. To prolong activity of the enzyme, the Chase used in this study was buffered in trehalose (which stabilizes proteins and helps retain the activity of enzymes) and embedded in lipid microtubes (which enable sustained release). Prior work in rodents indicates sustained local delivery for 6 weeks with this preparation, which is an advance from previous protocols that involved multiple repeat injections (e.g. Bradbury *et al.*, 2002). However, it is possible that even longer-term delivery may be necessary to achieve more significant functional improvements, as recent gene therapy studies in rodents suggest, where viral vector delivery of Chase enabled prolonged administration over many spinal segments (Bartus *et al.*, 2014). Other efforts are focused on generating mutated variants of Chase with improved thermal stability and mammalian compatibility, as well as pharmacological approaches to mimic the action of Chase, for example by inhibiting proteoglycan sulfation. It will be interesting to evaluate the efficacy of these emerging

therapeutics, as potentially they may have a faster route to gaining regulatory approval than the native Chase enzyme.

Of note however, there are several clinical trials, either active or completed, that have used a clinical grade preparation of bacterial Chase (SI-6603, generic name Condoliase) for the treatment of patients with lumbar disc herniation involving nerve root compression. A recent randomized, double-blind, multicentre Phase III trial successfully met its primary end point with significantly greater reductions in worst leg pain within 13 weeks in patients that received Condoliase injected into the intervertebral disc compared to patients with control injections; their one year follow-up suggests that Condoliase, at least when injected into a disc, is safe and well tolerated in this patient group (Chiba *et al.*, 2017). This is promising in the step towards clinical translation of Chase for spinal cord injury. Nevertheless, concerns remain over potential immunogenicity of this bacterial protein when injected into the central nervous system and de-immunization of the protein may be required, and/or rigorous pre-clinical testing to prove it is non-immunogenic, before regulatory approval is granted for clinical trials involving people with spinal cord injuries who are often immunocompromised.

In conclusion, this work shows it is feasible, sensitive and effective to evaluate candidate therapies for spinal cord injury in well-powered, blinded, randomized, controlled trials using a heterogeneous and relatively large cohort of naturally-injured large animals. These data shows that Chase is safe and effective in improving gait in another large species. Together with the positive human Phase III data for herniated lumbar discs, the Chase is on!

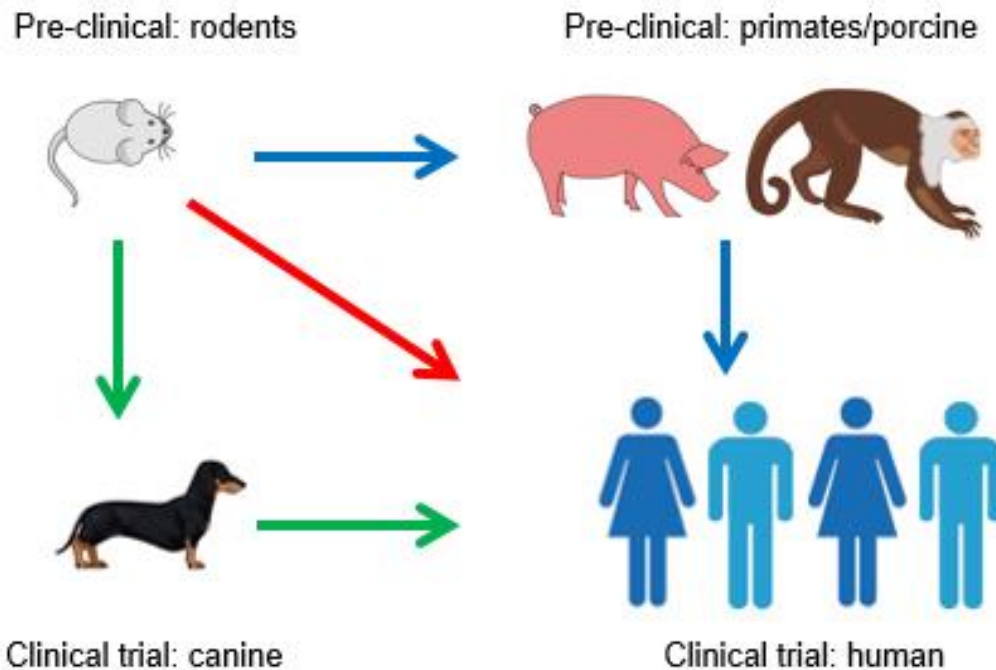


Figure 1 Route to clinical translation of Chase and other therapeutics for spinal cord injury.

There is a pressing need to advance experimental therapies for spinal cord injury to the clinic. However, the clinical translation of novel therapeutics for spinal cord injury is notoriously slow. The most direct route is to advance directly from small animal (mainly rodent) pre-clinical studies to human trials (depicted by red arrow) and this has been the route for several stem cell and pharmacological therapies. However, to date there has been limited clinical success, possibly due to the heterogeneity of the clinical population. There is merit in using large animal models prior to human trials and current therapies such as anti-NOGO-A antibody treatment (ATI-355: NCT00406016) and autologous human Schwann cells (ahSC: NCT01739023) have followed this route (depicted by blue arrows). These pre-clinical models can prove valuable for dosing, biodistribution and surgical refinement studies (e.g. the porcine spinal cord is similar in size to the human spinal cord) and for evaluating efficacy in a species closer to human (e.g. primates for studies of skilled hand function). However, these studies can be precluded due to prohibitive costs and ethical hurdles. Hu et al. used an alternative route to evaluate a promising experimental regenerative therapy (Chase). Based on preclinical basic research findings, derived largely from rodent models, they evaluated this therapy in a canine clinical population. This is a population of pet dogs who have sustained a spinal cord injury and can be enrolled in clinical trials at a veterinary research institution. This type of trial provides an opportunity to assess the potential of an experimental therapeutic in a clinical group with heterogeneous injuries of different severities, sustained at different spinal levels, and whose injuries are considered chronic since they were sustained at least 3 months prior to trial recruitment, when any spontaneous recovery would have reached a plateau. Thus, this population can serve as a model for the majority of patients living with spinal injuries. In a rigorous trial design, they demonstrated improvements in forelimb-hindlimb coordination on a treadmill in the treated

group and a small percentage of the treated dogs even recovered independent ambulation. Although these effects may appear modest, detection of benefit in real-life heterogeneous spinal injuries, with no observable adverse effects, represents a significant advance. The potential pathway from rodent basic research, to canine clinical trials and then human trials is depicted by green arrows and represents the possibility of reduced cost and accelerated progression of promising experimental therapies such as Chase to Phase I clinical trials in humans.

Glossary terms

- Chase (Chondroitinase ABC): a bacterial enzyme that degrades chondroitin sulphates.
- Chondroitin sulphate: growth inhibitory glycosaminoglycan sugar side chains that extend from a proteoglycan core protein.
- Neuroplasticity: the ability of axonal projections to sprout and form new synaptic connections following injury

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