Sciatic nerve injury model in the axolotl: functional, electrophysiological, and radiographic outcomes

Laboratory investigation

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Object. The 2 aims of this study were as follows: 1) to establish outcome measures of nerve regeneration in an axolotl model of peripheral nerve injury; and 2) to define the timing and completeness of reinervation in the axolotl following different types of sciatic nerve injury.

Methods. The sciatic nerves in 36 axolotls were exposed bilaterally in 3 groups containing 12 animals each: Group 1, left side sham, right side crush; Group 2, left side sham, right side nerve resected and proximal stump buried; and Group 3 left side cut and sutured, right side cut and sutured with tibial and peroneal divisions reversed. Outcome measures included the following: 1) an axolotl sciatic functional index (ASFI) derived from video swim analysis; 2) motor latencies; and 3) MR imaging evaluation of nerve and muscle edema.

Results. For crush injuries, the ASFI returned to baseline by 2 weeks, as did MR imaging parameters and motor latencies. For buried nerves, the ASFI returned to 20% below baseline by 8 weeks, with motor evoked potentials present. On MR imaging, nerve edema peaked at 3 days postintervention and gradually normalized over 12 weeks, whereas muscle denervation was present until a gradual decrease was seen between 4 and 12 weeks. For cut nerves, the ASFI returned to 20% below baseline by Week 4, where it plateaued. Motor evoked potentials were observed at 2–4 weeks, but with an increased latency until Week 6, and MR imaging analysis revealed muscle denervation for 4 weeks.

Conclusions. Multiple outcome measures in which an axolotl model of peripheral nerve injury is used have been established. Based on historical controls, recovery after nerve injury appears to occur earlier and is more complete than in rodents. Further investigation using this model as a successful “blueprint” for nerve regeneration in humans is warranted. (DOI: 10.3171/2008.10.JNS08222)

Key Words • animal model • axolotl • electrophysiological study • nerve injury • regeneration • sciatic nerve

Although functional reinnervation in humans may occur following peripheral nerve injury, it remains suboptimal.18 Human axonal regeneration is especially poor following transections far from the denervated muscle, and does not occur to a significant extent when the nerve roots are avulsed from the spinal cord.19 This relatively poor recovery after nerve injury is similar to all higher vertebrates, phylogenetically back to certain amphibians (for example, axolotls), which have retained the unique ability to regenerate lost limbs and heal spinal cord transections, even into maturity.5,7,32 In the axolotl, transected sciatic nerves displaced into the pelvis reliably reinnervate the appropriate limb.5 Furthermore, there is evidence that the anterior horn cells even reconnect with their original muscular contacts upon reinnervation.8,29 Axonal guidance clues are likely to play a significant role in this precise regeneration.16,28

It has been documented that guidance molecules active during embryonic axonal development are highly conserved back to and including many invertebrates (for example, Drosophila), and as organisms become more phylogenetically complex, axonal guidance mechanisms in general do not change, but instead become redundant.10 It is our hypothesis that, unlike in higher vertebrates, transected and displaced axons in adult axolotls follow embryonic mechanisms and environmental clues during axonal regeneration. We base this hypothesis on the following observations. First, axolotls can reform a functional and anatomically correct appendage follow-
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ing amputation.6,7 Second, morphologically and chemically similar limb regeneration can occur during specific stages of embryonic development in higher vertebrates (for example, mice).9 Third, multiple neurotrophic factors that play an important role in embryonic nervous system development are upregulated following peripheral nerve transection in the axolotl.23

Considering the fact that the axolotl model for nerve regeneration is new, the aim of these preliminary experiments is to establish functional, electrophysiological, and radiographic outcome measures of axolotl nerve regeneration to define the timing and completeness of reinnervation. Outcomes will be compared with historical controls in rodents for further confirmation that recovery after nerve injury in axolotls is, in fact, superior. Subsequent experiments using these outcome measures are planned to evaluate our hypothesis.

Methods

Experimental Design

Both Institutional Review Board (protocol H12257–01A) and Institutional Animal Care and Use Committee approval (protocol 041116–01) were obtained at New York University School of Medicine for this project, in which 36 adult axolots (Ambystoma mexicanum) 15–22 cm in length were used. The axolots, Holtfreter solution, and food pellets were all obtained from the Ambystoma Genetic Stock Center at the University of Kentucky. The animals were maintained in individual tanks filled with tap water and Holtfreter solution, with the water temperature maintained at 16°C. Standard diurnal lighting was provided and the animals were fed food pellets 2 times per week.

Bilateral sciatic nerves were surgically exposed in all 36 axolots. Experimental groups included the following (12 animals/group): Group 1, left side—exposure only (sham control), right side—sciatic nerve crush injury; Group 2, left side—exposure only (sham control), right side—1 cm of sciatic nerve resected and proximal stump buried in proximal leg musculature; Group 3, left side—sciatic nerve cut and repaired with 2 sutures, right side—sciatic nerve cut and repaired, but the tibial division was sutured to the peroneal division, and the peroneal division was sutured to the tibial division. The main outcome measure was functional swim analysis, with both electrophysiological and radiographic evaluations being performed to support these results.

Surgical Procedures

All surgical procedures were performed after induction of deep anesthesia attained by immersing the axolotls in an aqueous solution of 0.2% benzocaine (Fisher Scientific). A dissecting microscope was used for each procedure (Stemi DV4, Zeiss). The axolotls were kept moist throughout the procedure by covering them with disposable towels moistened with anesthetic solution. The region of the incision was sterilized using chlorhexidine solution (Zila Pharmaceuticals). A 1-cm incision was created along the posterior-dorsal thigh with a No. 15 scalpel blade, and the skin and hamstring musculature were gently retracted using a modified paperclip retractor. The sciatic nerve, along with the tibial and peroneal divisions, was exposed over a total length of 1 cm. The sciatic artery was visualized in all animals and meticulously preserved throughout the procedure.

Crush injuries were performed by grasping the complete sciatic nerve with a jeweler’s forceps and firmly squeezing the instrument for 30 seconds. For resected nerves, 1 cm of the sciatic nerve was removed with microscissors. During this removal the sciatic artery was uninjured, which is paramount to preserving the limb. The proximal stump of the nerve was then buried in the proximal thigh musculature and secured in the muscle by using a single 10-0 nylon suture (Dermalon) (Fig. 1). For cut and repaired nerves, the tibial and peroneal divisions of the sciatic nerve were first identified prior to their transection with microscissors. These divisions were then immediately repaired using a single 10-0 nylon suture (Dermalon) (Fig. 1). Wounds were closed with a running 4-0 Polysorb suture (Autosuture). Electrodiagnostic studies were performed during the surgical procedures (see below). After surgery, each axolotl was kept at 4°C for 24 hours, which prevents vigorous activity.

Prior to planned death, each axolotl was once again anesthetized with benzocaine, and both sciatic nerves were surgically exposed for microscopic inspection and intraoperative electrodiagnostic testing. Once this was complete, the axolotls were immersed in a double dose of anesthetic solution and then euthanized. The surgical site, spinal cord, nerve, and muscle samples were collected and frozen at −80°C for use in subsequent experimental studies.

Swim Analysis (ASFI)

Kinematic measurements of the axolotl swim stroke were performed to assess functional recovery after nerve injury. Measurements of bilateral hindlimbs were obtained in all animals both prior to experimental sciatic nerve injury and then subsequently at 0.5, 1, 2, 4, 6, 8, and 12 weeks after injury. Our analysis technique was extrapolated from previous video gait analysis methods in rats following sciatic nerve injury.25

Fig. 1. Operative photographs of axolotl hindlimb. Left: Exposed sciatic nerve (asterisk) prior to experimental nerve injury (right hindlimb; distal is on the right side of the panel). Right: In Group 2, 1 cm of the right sciatic nerve was resected and the proximal stumps were buried in the musculature and secured with a suture (arrow). Original magnification × 16.
The axolotl to be examined was placed in a swim tank that was designed to produce continuous unidirectional (from cranial to caudal) water flow (Fig. 3). By using a flowmeter attached to the swim tank, the water flow was kept slow and constant at 10 L/minute, which stimulates the axolotl to make rhythmic swim strokes with its limbs. A digital video camera (Elura60, Cannon) was used to record the ventral surface of the axolotl, including both hindlimbs, via a mirror angled at 45°. The video was then transferred to a computer (PowerMac, Apple, Inc.), where select images were captured so that hindlimb joint angles could be measured. The following measurements were tabulated using ImageJ software (NIH): maximum hip, knee, and ankle ROM as well as toe spread distance (Fig. 4). Dividing by the adjacent ankle width normalized the latter.

Hindlimb ROM measurements were then used to create an ASFI based on the methodology previously used by Bain et al. for the SFI in rats. Normal sciatic nerve function was defined as an ASFI of 0 and a complete sciatic palsy was defined as −1.0. The following equation template was used: ASFI = [x(knee ROM %change)] + [y(ankle ROM %change)] + [z(toe spread %change)]. Coefficients (x, y, z) for the ASFI equation were established by using the hindlimb measurements from 10 axolotls (from the current experimental groups) before and immediately after sciatic nerve transection (that is, complete loss of sciatic nerve function). In brief, ANOVAs (JMP statistical software, SAS Institute) were calculated for hip, knee, ankle, and toe spread measurements (Fig. 5).

Because a sciatic nerve injury in the thigh should not affect hip movement directly, this measurement was used as an internal control. Following a complete sciatic nerve injury, there was a statistically significant reduction in knee ROM (p < 0.0001), ankle ROM (p < 0.0001), and toe spread (p < 0.0001); hip ROM remained statistically un-
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changed (p = 0.32). Multiple linear regression analysis of these factors as independent variables against the dependent variable of the defined sciatic nerve injury resulted in the generation of indices x, y, and z. Please refer to Bain et al.2 for further details on these methods. Prior to its use in this study, the final equation, ASFI = [0.57(knee ROM %change)] + [0.37(ankle ROM %change)] + [1.23(toe spread %change)], was evaluated for accuracy by using paired measurements obtained over 12 weeks in 10 axolotls (from the current experimental groups) who underwent crush injuries of the sciatic nerve (data not shown).

Electrophysiological Analysis

Once the sciatic nerves were exposed (or reexposed at subsequent time points), direct electrophysiological evaluation was performed. A custom-made platinum microbipolar electrode connected to a stimulus isolator (ML180, ADInstruments) was used to stimulate the nerve. No paraffin or wax was used. This was repeated 10 times; that is, once every 20 seconds. A second microbipolar electrode connected to a signal conditioner (ML136, ADInstruments) recorded the CMAP on the plantar aspect of the axolotl foot 2 cm distal to the stimulus, as measured with a small measuring tape in each hindlimb. The latency until a CMAP began was measured in milliseconds, and averaged over 10 recordings for each hindlimb by using a Powerlab data acquisition system and Chart software (ADInstruments). Recordings were graphically depicted with a time base of 2 msec and an amplitude scale of 1 mV. Based on the experimental group, the results were averaged for all hindlimbs evaluated at each time point. Trends in motor latencies for each of the experimental groups were then plotted over 12 weeks and compared with the baseline mean, which served as a control. Statistical analysis was not performed because only 2 axolotls in each experimental group per time point were euthanized for evaluation.

Radiographic Analysis

Six axolotls (2 from each experimental group) underwent MR imaging of the distal hindlimb musculature as well as the injured sciatic nerve. The MR imaging studies were performed before experimental nerve injury, and then at 1, 2, 4, and 12 weeks. The same 6 axolotls were evaluated throughout the study period. They were sedated with aqueous benzocaine, wrapped in a moist cloth, and then placed prone inside a standard wrist coil. A 3-T MR imaging unit was used (Siemens). The imaging protocol included axial images perpendicular to the long axis of the axolotl’s body. Contrast material was not used. Three sequences were acquired, based on previous experimental reports: TIRM (TR 6250 msec, TE 40 msec, TI 320 msec, ST 4 mm); T2-weighted (TR 7600 msec, TE 147 msec, ST 4 mm); and PD (TR 2200 msec, TE 34 msec, ST 3 mm).3,4,13,14,21,22,26

Image analysis was performed using Osirix DICOM software (Osirix Foundation). Based on the known location of the sciatic nerve in relation to the easily identifiable tibia and fibula,15 a 1-mm² voxel of interest was chosen over the sciatic nerve just distal to the knee joint (that is, distal to the site of experimental nerve injury). The signal intensity in arbitrary units within this voxel of interest was measured and normalized to the contralateral limb, which represented an experimental control (sham surgery in Groups 1 and 2, and uncrossed sciatic divisions in Group 3). Measurements were repeated 5 times in each limb for each of the 2 axolotls from each experimental group, with the results being averaged. To evaluate muscle denervation a similar protocol was used, but the voxel of interest was centered in the plantar flexor muscle mass in the lower limb, which is innervated by the sciatic nerve. Once again the results were averaged and normalized against the contralateral limbs for Groups 1 and 2. Because both hindlimbs in Group 3 underwent nerve transection, these results were normalized to the ipsilateral iliopsoas muscle. Trends were plotted over 12 weeks for each imaging sequence and experimental group. A pictorial overview of the MR imaging methods is presented in Fig. 6. Considering the fact that only 2 axolotls were used per group, statistical analysis was not performed and only trends are presented.

Results

Functional, electrophysiological, and radiographic
outcome measures in the axolotl after different types of sciatic nerve injury have been established. The timing and completeness of recovery have been documented for crush injuries (Group 1), buried proximal nerve stumps (Group 2), and transection injuries (Group 3) to the axolotl sciatic nerve.

No axolotl developed wound infections, automutilation, or died during the course of the experiment. Mild flexion contractures of the knee (that is, ~20°) occurred in the hindlimbs in which the cut sciatic nerves were resected and buried in muscle. No contractures occurred in any of the hindlimbs that underwent crush injuries or in those in which the sciatic nerves were cut and repaired. Postoperative limb sloughing did not occur, presumably because the sciatic artery adjacent to the sciatic nerve was meticulously preserved in all hindlimbs.

Swim Analysis

Partial or complete recovery of hindlimb function occurred in all experimental groups. Recovery trends evaluated using the ASFI are presented in Fig. 7. In summary, hindlimb movement had returned to normal following crush injuries (Group 1) by 2 weeks. Nerves that were cut, resected, and buried (Group 2) demonstrated early signs of recovery at 6 weeks, with a recovery to ~80% of normal by 8 weeks. After nerves were cut and repaired (Group 3), hindlimb function returned to ~80% of normal by 4 weeks, after which it plateaued. Switching the sciatic nerve divisions at the time of repair caused a 3-week delay in recovery to ~80% of normal. Once recovery had plateaued, the ROM and fluidity of swim stroke appeared similar regardless of whether the divisions were switched.

Electrophysiological Analysis

The return of recordable evoked potentials paralleled the functional outcomes seen with the swim analysis. Trends in motor latency over the 12-week study period as well as example tracings are depicted in Fig. 8. In summary, for crush injuries (Group 1) the evoked potentials were never lost, but had an increase in the motor latency for ~2–3 weeks. Sciatic nerves that were resected and then their proximal stump buried in muscle (Group 2) lost their evoked potential until 8 weeks after injury. This positive result paralleled the functional recovery seen in this group at 8 weeks by using swim analysis. After nerves were transected and repaired (Group 3), the evoked potential was also initially lost. For sciatic divisions that were repaired in the correct orientation, an evoked response was observed between 2 and 4 weeks after injury, with an increased motor latency. For sciatic divisions that were repaired with a reversed orientation, a return of the evoked potential was delayed by an additional 4–6 weeks. When an evoked potential did return in hindlimbs in which the sciatic divisions were reversed, a more dispersed, polyphasic CMAP was observed.

The MR Imaging Analysis

High-resolution TIRM, T2-weighted, and PD images were obtained in all animals imaged at each of the time points. Results for each of these sequences as a percent change from either the contralateral control limb or ipsi-
lateral psoas muscle are presented using trends over the 12-week study period (Fig. 9). Although results are presented for each of the 3 sequences used, based on the recommendation and results of previous studies in rats,21,22 the TIRM sequence was chosen a priori to evaluate nerve edema distal to the nerve injury, as was the T2 sequence for the evaluation of muscle edema. In summary, for Group 1, nerve edema distal to the crush injury was elevated 40% above that in the hindlimb that underwent sham surgery; this elevation lasted for 2 weeks. Muscle edema also increased compared with the control limb, but returned to normal between 2 and 4 weeks after injury. For sciatic nerves that were resected and buried (Group 2), distal nerve edema was elevated for ~ 2 weeks compared with the contralateral hindlimb that underwent sham surgery. Muscle edema in Group 2, however, remained elevated for much longer, trending toward baseline between 4 and 12 weeks after injury. Because there were no images obtained between these 2 time points, a more precise timing of the muscle edema resolution was not possible. Because both hindlimbs underwent nerve transection in Group 3 (with the sciatic divisions switched in 1 prior to suture repair), the percent difference in nerve edema distal to the transection was presented as the percent difference from switch to no switch. In this group, muscle edema was normalized to the ipsilateral iliopsoas muscle instead of the contralateral limb, explaining the 10-fold increase in the percent difference seen in these animals compared with the other groups. For Group 3, distal nerve edema was higher in the hindlimbs in which the sciatic divisions were switched before repair. An increase in muscle edema was seen for both the switched and unswitched sciatic divisions; however, the amount of muscle edema was greater in the hindlimbs in which the divisions were switched.

**Discussion**

Most research on nerve injury and regeneration has relied on the use of murine experimental models. However, like humans, rats and mice demonstrate poor or no recovery following some severe peripheral nerve injuries.5,17,24,27,31 In light of this, our goal was to establish a model of regeneration after nerve injury that would represent a gold standard; that is, a model with near complete, functional regeneration even after the most severe injuries. This model would then be used as a blueprint for optimizing regeneration in higher vertebrates, like rats, mice, and humans. Phylogenetically, the most advanced species that can be used as such a model is the urodele salamander (axolotl; genus *Ambystoma*). The unique regenerative capacity of their amputated limbs, along with their relatively large size (similar to a rat), has led to their use in the fields of tissue regeneration and wound healing.5,7 In several studies axolotls have been found to have a remarkable ability to recover after spinal cord and peripheral nerve injury,5,30,32 however, standardized use of the axolotl as a model for nerve regeneration has not been reported.

Two prerequisites for an axolotl model of nerve injury were to define reproducible outcome measures and...
to confirm that recovery after nerve injury in the axolotl is superior to the rat or mouse. As with murine models, functional, electrophysiological, and radiographic outcome measures are all important, not only to evaluate recovery independently, but also to corroborate each outcome (for example, confirming a functional recovery by documenting the muscle action potential). Without easily reproducible outcome measures, the axolotl model of nerve regeneration would not be practical. In our current study, we have documented these outcome measures in the axolotl after nerve injuries of varying severity, and have also shown that axolotl recovery, when compared with historical controls in rodents, is indeed more rapid and complete.

Two factors made it possible for known murine outcome measures (movement analysis, electrophysiological studies, and MR imaging) to be easily modified and used in the axolotl. 1) The axolotl and its limbs are similar in size to a rat. The axolotl’s peripheral nerves are large enough to undergo microsurgery, electrophysiological assessment can be performed using CMAPs, and neuromuscular MR imaging is possible by using standard human wrist coils. 2) The complex motion of the axolotl hindlimb, including hip, knee, and ankle ROM, along with digit spread, allows application of an ASFI, extrapolated from past experimentation in rats. The SFI is a proven and commonly used functional outcome measure for documenting recovery after peripheral nerve injury. We have documented that ASFI values returned to baseline by 2 weeks after crush injury, that transected and sutured sciatic nerves reached 80% of baseline by Week 4, and that resected and buried nerves took ~ 8 weeks to return to 80% of baseline. In contrast, Varejao and colleagues used walking track analysis in rodents to report a normalization of rat SFI values by 8 weeks after crush injury, whereas Luis et al. recently documented that end-to-end sciatic nerve repair in the rodent resulted in an incomplete functional recovery (40–50% of baseline, depending on outcome measure) by 10–12 weeks. Similar results after crush and transection injuries in a murine model have been reported by other authors. Although we acknowledge that the timing of recovery after crush injury may be variable due to poor standardization of experimental crush injury, multiple outcomes remain markedly better in the axolotl when compared with rodents. For example, the axolotl recovered quicker (1 compared with 4 months) and more completely (80% compared with 40–50%) after nerve transection and suture repair. Furthermore, axolotls recovered after their sciatic nerves were transected without repair, even when 1 cm of the nerve was resected and the proximal stump was buried in muscle and sutured in place (Fig. 10). Confirmation of

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**Fig. 7.** Graph showing outcomes assessed using the ASFI to evaluate limb function after different types of experimental sciatic nerve injury. An index of 0 represents normal function, whereas −1 represents no sciatic nerve function. (For simplicity, results for sciatic nerves that were cut and their divisions switched were omitted in this figure.)

**Fig. 8.** Graphs showing CMAP and motor latency results. 

A: An example of a crush injury in which during the 1st week the evoked potential was present but with an increased latency. 

B: When the sciatic nerve was cut and its divisions repaired in the proper orientation, the evoked response was lost, but returned by 2 weeks, with the amplitude subsequently increasing over time.

C: When the sciatic nerve was cut and its divisions repaired after they were switched, the reappearance of an evoked response was delayed between 4–6 weeks. When it did return, it remained more polyphasic and with greater temporal dispersion compared with the other types of nerve injury, even at the 12-week time point.

D: Sciatic nerves that were resected and buried had a return of evoked potentials by 12 weeks. These axolotls also had small, albeit reproducible, evoked responses by 8 weeks (arrow).

E: Presence of evoked potentials and trends in motor latencies over time for each injury type. These results paralleled the ASFI results presented in Fig. 7. Hindlimbs that underwent sham surgery were used as controls (mean motor latency 2.98 msec [SEM: 0.55 msec]).
this superior ability to recover after peripheral nerve injury is warranted in future studies in which the axolotl is used.

Electrophysiological outcomes in axolotls were also superior to those in rats. For example, Varejao and colleagues reported that motor nerve conduction velocities in rats maintained a 43% deficit 8 weeks after crush injuries in their series, whereas the motor latency in axolotls normalized by ~ 2 weeks postcrush. Following nerve transection and repair, the presence of motor evoked potentials 2 weeks postinjury were a clear electrophysiological sign of rapid axonal regrowth in the axolotls (Fig. 8B). Similar to rats, nerve-to-nerve action potential recordings are difficult to perform in axolotls because only ~ 1 cm of nerve can be exposed in the posterior thigh. Variability in CMAP amplitudes and areas under the curve was present in the control limbs despite standardization of electrode placement, and therefore only motor latencies as well as the presence versus absence of a reproducible response were used as the electrophysiological outcome measures in the axolotls.

Our MR imaging results parallel the functional results seen with ASFI. The MR imaging studies demonstrate edema after peripheral nerve injury, with resolution of hyperintense signal on TIRM (distal nerve edema) and T2-weighted images (denervated muscle edema) being previously correlated with electrophysiological findings and walking track analysis in rats. Following crush injuries in axolotls, distal nerve edema seen on TIRM sequences normalized by 2 weeks, whereas increased signal intensity in crushed rat nerves takes ~ 4–6 weeks to resolve. With nerve transection and repair in the axolotls, T2-weighted sequences revealed an increase in muscle edema (denervation) for 4 weeks, after which it plateaued near that of the control muscle. In rats, increased T2 signal intensity in denervated muscle persisted at a peak level for at least 3 months after end-to-end repair. Because we only used 2 axolotls per experimental group for MR imaging analysis, our results simply confirm that this technique is feasible, and provide preliminary evidence that edema resolves more rapidly in these animals than in rodents.

As part of a future study on axonal guidance and correctness of reinnervation, in 1 hindlimb for each axolotl in experimental Group 3 the sciatic nerve divisions were switched prior to end-to-end repair. Using the contralat-
eral unswitched sciatic nerve as a control, switching the divisions caused an approximate 3-week delay in ASFI-documented recovery. When the CMAP returned in the switched hindlimb, it demonstrated greater temporal dispersion and a more polyphasic response (Fig. 8C). This may be consistent with a more dispersed or erroneous reinnervation pattern. Additional nerve and muscle edema was also seen in the switched hindlimbs on MR imaging analysis. It remains uncertain if these regenerating axons prune and subsequently regenerate down the correct division, establish a new pattern of muscle innervation, or whether the temporal dispersion may resolve with longer follow-up (that is, longer than our end point of 12 weeks). Although not presented in this report, retrograde labeling of axons and cell bodies was performed prior to planned death. These data will be subsequently analyzed in light of the functional, electrophysiological, and radiographic results obtained from experimental Group 3.

The establishment of an axolotl model of regeneration creates the opportunity to investigate the fundamental mechanisms underlying such an optimal recovery following a range of peripheral nerve injuries.8,28–30 Our methods and results also represent the initial development of the axolotl as a functional model for spinal cord and cerebral regeneration following ischemia or trauma. A more comprehensive understanding is needed of the regulatory pathways that axolotls use to reestablish a functional and anatomically correct appendage following amputation, and how this is morphologically and chemically similar to limb regeneration during specific stages of embryonic development in higher vertebrates. Because nerve growth factors and axon guidance molecules are highly conserved over species,10 we hypothesize that their concerted up- and/or downregulation during regeneration may be similar to what occurs during embryonic peripheral nerve development.23

Conclusions

Multiple outcome measures have been established using an axolotl model of peripheral nerve injury. Recovery after nerve injury appears to occur earlier and is more complete than in rodents. Further investigation using this model as a successful blueprint for nerve regeneration in humans is warranted.

Disclosure

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