A Systematic Review of Animal Models Used to Study Nerve Regeneration in Tissue-Engineered Scaffolds
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Introduction
The use of animal models is a critical experimental phase in the testing of nerve scaffolds prior to implementation in clinical practice. We provide an overview of the more commonly used and readily available animal models for the evaluation of nerve regeneration into synthetic conduits. A scientifically valid animal model of nerve regeneration requires that the model reproduces specific pathologic processes which take place in human peripheral nerve injury. Although animal models might closely mimic the mechanical and physiological human clinical conditions, one must always consider that these models represent an approximation of the human response to pathologic factors. Each animal model has distinctive benefits and drawbacks when used in any experimental study of nerve injury.

Methods and Materials
Inclusion criteria
Inclusion criteria: (1) in vivo experimental study, (2) animal species used as experimental model (human clinical studies have not been included), (3) use of a synthetic nerve conduit (biodegradable material or not), and (4) article written in English. Exclusion criteria: (1) absence of a gap between the proximal and distal stump of the injured nerve, (2) use of an autologous or heterologous tissue (vein, artery, muscle, nerve, perineurium) as material to synthesize the nerve scaffold. Selection of Articles
Titles or abstracts were evaluated for inclusion. For each eligible study, two reviewers extracted all available and relevant data for the experimental groups. These data included demographic and physical information about the animal model used (species, weight and gender), the number of animals included, the injured nerve model, the type of material used, the length of the gap and the nerve scaffold, the characteristics of the experimental groups, and the assessments performed.

Results
The literature search on animal models yielded 385 studies that met the inclusion criteria. The animal models studied include: rats (n = 283); rabbits (n = 30); mice (n = 30); cats (n = 14); dogs (n = 13), monkeys (n = 10), sheep (n = 4) and guinea pigs (n = 1). The nerve models investigated were: sciatic (n = 283); peroneal (n = 28); tibial (n = 21); facial (n = 21); median (n = 13); radial (n = 6); ulnar (n = 5); alveolar (n = 5); cavernous (n = 3); and saphenous (n = 2). The sural, optic, phrenic, hypogastric, recurrent laryngeal and lingual nerves were each chosen in one study. The length of the gap grafted by a synthetic scaffold was between 1 mm and 50 mm in the rat model; between 2 mm and 13 mm in the mouse model; between 2 mm and 50 mm in the rabbit model; between 10 mm and 90 mm in the dog model; between 1 mm and 50 mm in the cat model; and between 1 mm and 50 mm in the monkey model. In the pig model the gap was 8 mm, and no gap was present between the distal and the proximal stump in the sheep model. The materials used to fabricate the nerve scaffolds were classified in four groups based on their chemical and biological characteristics: inorganic (n=4), natural organic (n=95), synthetic organic nondegradable (n=255), and synthetic organic degradable (n=108). The assays performed to evaluate nerve regeneration have measured an extensive number of experimental parameters generating a large database. They included 15 different major types of assessments.

Discussion and conclusion
On the basis of our present knowledge, it is clear that each of the species reviewed shows distinctive advantages and disadvantages in terms of their suitability as a model for axonal regeneration into an implanted synthetic conduit. Even if non-human primates are often believed to be the most comparable and reliable animal model for human nerve regeneration, there are ethical issues in using these species for medical research as well as economical and management issues, and the risks of zoonotic disease. Of the species investigated the rodents represent a more economical and tested species for nerve repair, however the size and the differences in neurobiological process after primary nerve repair should be considered carefully before any attempts of translation of such results into clinical practice. Large mammals may exhibit more similar nerve structure and biology to humans, however, they may cause housing, handling and availability issues, as well as difficulties with functional assessment and ethical concerns. While no distinct animal species meets all the requirements for an ideal animal model, a deeper comprehension of the differences in nerve macroscopic, microscopic and regenerative neurobiology may help improve the selection of animal species, as well as the analysis and translation of these results to human disease.

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Disclosures
No conflict of interest disclosure information in this work.