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Review Article

From rodents to pigs: critical evaluation of animal models in cutaneous wound healing research studies

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ABSTRACT

Animal models are vital to elucidate the mechanisms of skin wound repair and to evaluate new-fangled therapeutics in preclinical setting. However, the choice of model has a profound effect on translational relevance. This review synthesizes evidence from key methodological and comparative studies for a critical evaluation of strengths, limitations and appropriate use of commonly used animal models, in particular rodents, pigs and companion animals. We highlight the importance of matching the choice of models to specific research questions, wound pathophysiology and desired clinical outcomes.

Keywords: Rodents, Mice, Rat;pig, Incision model, Excision model,Wound healing

INTRODUCTION

Wound repair is a dynamic, multicellular process that involves haemostasis, inflammation, proliferation and remodelling.[1] Researchers rely on a range of "*in vitro*" and "*in vivo*" models to study this process.[2] While in vitro systems (e.g. monolayers, 3D skin equivalents) provide mechanistic insight under controlled conditions, in vivo models are still necessary to capture the complexity of tissue repair, immune responses and systemic effects.[2,3]

However, not all animal models recapitulate the same process of healing a human injury.[3] Species-specific differences in skin anatomy, immune function and wound healing kinetics-especially the dependence on contraction of the wound rather than re-epithelialisation-may limit the clinical extrapolation.[4,5]

This review assesses the most commonly used animal models based on evidence from the seminal and recent literature in the peer reviewed journal, with a focus on translational fidelity.

RODENT MODELS: UTILITY AND LIMITATIONS

The most frequently used species for wound healing research studies are mice and rats because of their low costs, short recovery times and extensive genetic tractability.[4-6] Transgenic and knockout models allow for a precise breakdown of the molecular pathways, such as the role of TGF-beta, VEGF and IL-1 cytokines.[7]

However, the main limitation is their dependence on "*panniculus carnosus*", a subcutaneous muscle layer that is not present in humans[4-7], for wound contraction. This results in a rapid closure, which is poorly mimicked in human healing, which is mainly achieved by re-epithelialisation and granulation (Figure 1).[4-7]

To address this, cutaneous models of excision wounds have been developed, in which a silicone or polyurethane ring is placed around the full thickness of the wound to prevent contraction and force the healing by secondary action.[5-7] This change significantly improves the clinical relevance and is now considered as good practice in chronic or regenerative healing studies in animals.[5-7]

Despite these advances, rodent skin is still thin, highly vascularized and immunologically different from human skin, which limits its predictive value in complex injuries (e.g. diabetic, ischemic).[5-7]

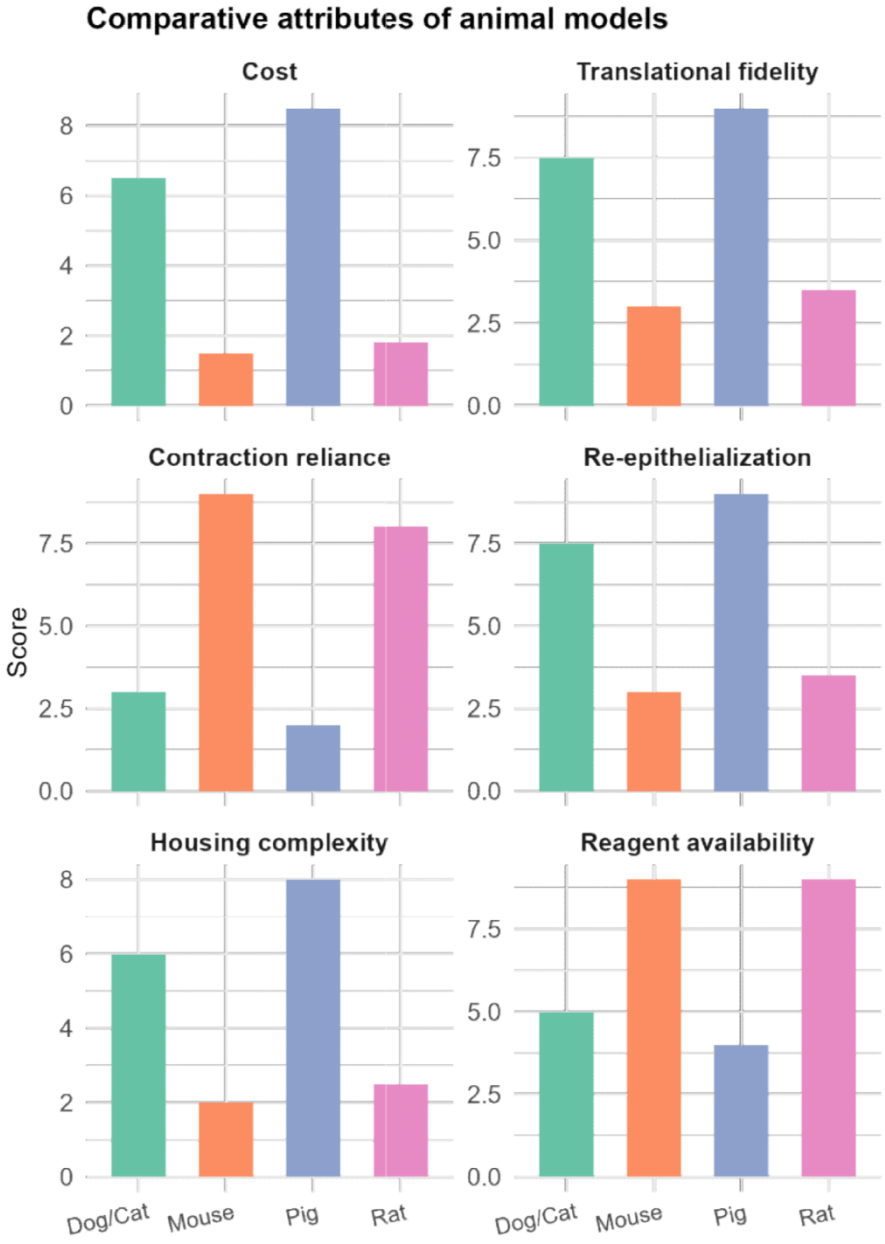

Figure 1: Animal attribute and comparison.

PORCINE MODELS: THE GOLD STANDARD FOR TRANSLATIONAL RESEARCH

The domestic pig (*Sus scrofa domesticus*) is generally considered the best model for the cutaneous wound healing models.[8] Pig skin is analogous to human skin in: thickness and structure of the epidermal layer, collagen and elastin content, density of the follicle (sparse, like human skin), and healing kinetics dominated by re-epithelialization, rather than contraction.[8,9] Sullivan et al showed that pig wounds exhibit histological, biochemical and pharmacological responses to treatment that are very similar to those of humans, which makes pigs ideal for testing skin substitutes, growth factors and bioengineered skin.[8]

In addition, pigs support partial thickness wound models, which are necessary to study the re-epithelialisation of hair follicles and sweat glands, which are not present in

rodents.[4-8] This ability is essential for evaluation of regenerative therapies aimed at restoration of skin tissue.

The disadvantages include high costs, ethical considerations, specialized accommodation requirements and limited availability of specific agents for the species.[4-9] However, the pig remains unmatched for late preclinical validation (Figure 1).

COMPANION ANIMALS: EMERGING MODELS WITH HIGH CLINICAL FIDELITY

Dogs and cats offer unique benefits as models for chronic wounds. In contrast to induced wounds in laboratory animals, companion animals often develop naturally occurring chronic wounds (e.g. diabetic ulcers, pressure ulcers) in an outbred, immune-competent host that shares a human environment.[10]

Enciso and colleagues showed that allogeneic adipose-derived stromal cells significantly accelerated healing in both acute and chronic wounds in canine, and histological evidence of regeneration, including hair follicle and sebaceous gland was observed rarely in rodent models.[10]

Volk and Bohling argue that companion animals bridge the gap between controlled laboratory studies and human clinical trials and offer a higher predictive value for cellular and biological therapies.[10-15]

However, regulatory, ethical and logistical problems limit their wide-spread use.[10]

SPECIALIZED MODELS FOR IMPAIRED HEALING

For diabetic, ischemic or pressure ulcer research, standard models should be adapted: diabetic models: diabetic rodents induced by streptozotocin are common but exhibit variable wound phenotypes.[3-10] Genetically diabetic mice (e.g., db/ db) provide a more consistent pattern.[3-10]

Ischemic wounds

Models of rabbit ear or murine ischemic flap (e.g., Sisco and Mustoe, 2003) produce a hypoperfusion of tissue mimicking a venous stasis ulcer.[11]

Pressure ulcers

Rats and pigs using cyclic pressure loading devices replicate the deep tissue injury observed in patients with spinal cord injury.[12] Each of these requires careful validation to ensure that it is of pathophysiological relevance (Figure 2).

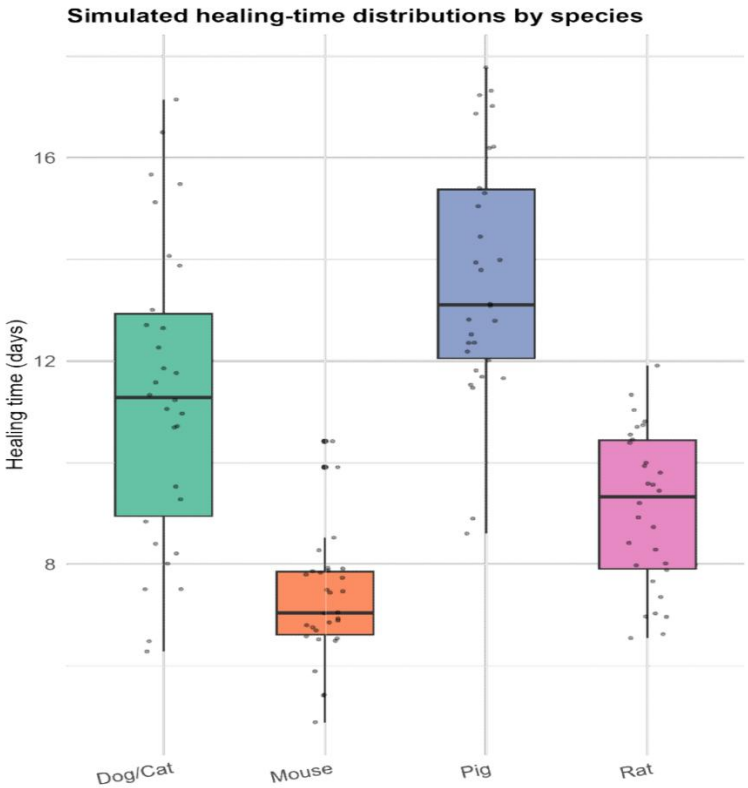

Figure 2: Healing-time species distribution.

RECOMMENDED MODEL FOR WOUND HEALING STUDIES

Lindblad and Conn stress the need for a purposeful approach in the selection of models.[13,14]

Key points to be considered include: Wound type (acute vs. chronic, full- vs. partial-thickness), healing mechanism of interest (contraction vs. re-epithelialization), therapeutic modality (small molecule vs. biologic vs. cell therapy), regulatory requirements (e.g., FDA often requires data from 1 rodent and 1 non-rodent species).[14-16]

A plurispecies strategy using rodents for mechanistic discovery and pigs or dogs for validation maximizes both scientific insight and translational impact.[14-16]

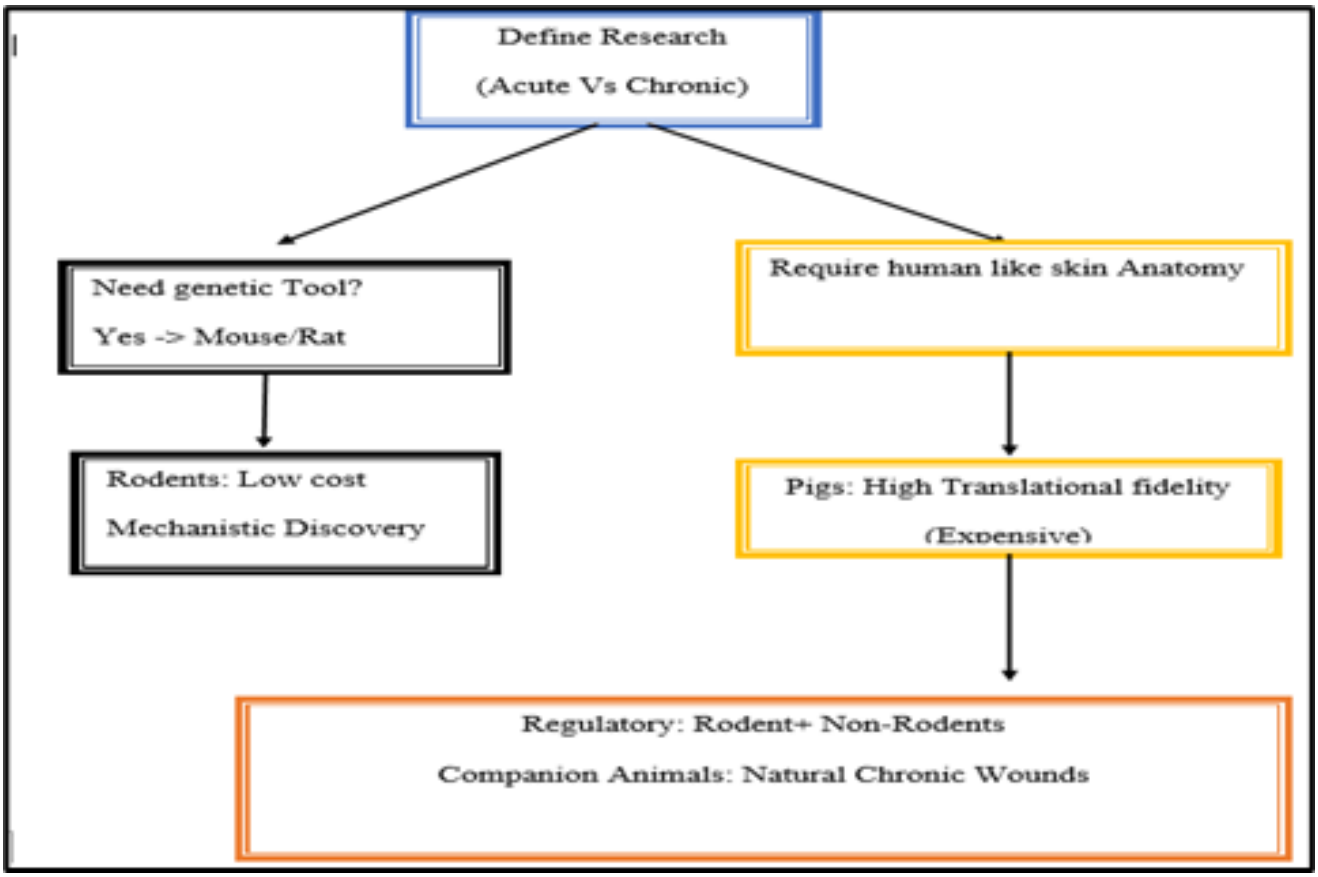

Figure 3: Decision to select an animal model.

CONCLUSION

No single animal model perfectly describes the healing of human wounds. Rodents offer genetic accuracy but poor anatomical fidelity; pigs offer high clinical relevance but higher costs; companion animals offer natural disease complexity but limited scalability. Researchers need to be careful in matching the choice of models with research objectives.

Future efforts should standardise reporting (e.g., strain, age, gender, wound size) and favour models that emphasise re-epithelialisation and regeneration over contraction in order to improve the predictability of the clinical outcome.

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