WVU IACUC Model Guidance Sheet: Rheumatoid Arthritis

Purpose

Rheumatoid arthritis animal models are used to study disease process and treatments for this debilitating autoimmune disease. It is characterized by synovitis leading to cartilage and bone erosion. Rheumatoid arthritis is a disease characterized by joint inflammation which causes pain and mobility issues in people. There are several commonly used models to induce disease in rodents. It is important to consider humane endpoints and clinical support when using working with this disease model.

Definitions

Polyarthritic- Systemic response involving multiple joints

Monoarthritic- Localized to a single joint

Hyperalgesia- An increased sensitivity to the feeling of pain and an extreme response to pain

Allodynia- Pain due to stimulus that does not normally provoke pain

Guidance

1. **Induced Models**
   a. Adjuvant-induced arthritis
      i. Classic arthritis model. Rats are predominantly used. Effects vary based on rat strain
         – High Responder Strains: Lewis, Sprague-Dawley (SD), Wistar, Brown Norway (BN)
         – Medium to Low Responder Strains: Buffalo (BUF), Fisher 344 (F344), Diabetic-resistant Subline of Diabetic BB (DR BB)
         – Resistant Strain: Wistar Furth (WF)
      ii. Induced via a single subcutaneous injection of Complete Freund's Adjuvant (CFA) into hindfoot or tail
   b. Collagen-induced arthritis (CIA)
      i. First developed in rats and adapted to mice; develops an acute to subacute monophasic erosive polyarthritis
      ii. Model response will vary with age, sex, and strain; tends to be more severe in males; optimal age is 8-12 weeks, should not exceed 10-14 weeks as severity of disease response decreases after that point
         – DBA/1 males are most appropriate for this model
      iii. Model induced using type II collagen emulsified with CFA followed by a booster 3-4 weeks later with type II collagen emulsified with Incomplete Freund's Adjuvant (IFA); inflammation will develop in the mouse paws 4-10 days after the booster
         – Model may vary with composition of oil used in CFA/IFA formulation

iv. The injections are administered intradermally (ID) at the base of the tail. Hair should be removed around this site prior to injection. Recommend administering 100 ul volume of emulsion to area. A bulge will form at the site of administration and this can be gently rubbed to promote absorption. Skin lesions (granulomas) may form at the site of CFA administration.
v. Collagen Antibody induced arthritis
   - Monoclonal antibodies against type II collagen used to induce model
   - Antibodies are commercially available
   - More abbreviated timeline for disease development
   - Antibodies may be administered with lipopolysaccharide (LPS)
   - Follow manufacturers instructions for disease induction

2. **Spontaneous Models**
   a. Multiple strains are available that spontaneously develop arthritis
   b. Strains for this model include: inbred strains prone to spontaneous arthritis (often polygenic), targeted genetic engineered mice (anti-inflammatory suppression or upregulation or pro-inflammatory mediators)
   c. Transgenic models
      i. K/BxN model
         - Serum from these animals can induce arthritis in other strains
         - May require a lot of mice to get enough to test
      ii. TNF-transgenic model
      iii. HTLV
      iv. GP130
      v. IL-ra-/-
      vi. IL-1tg

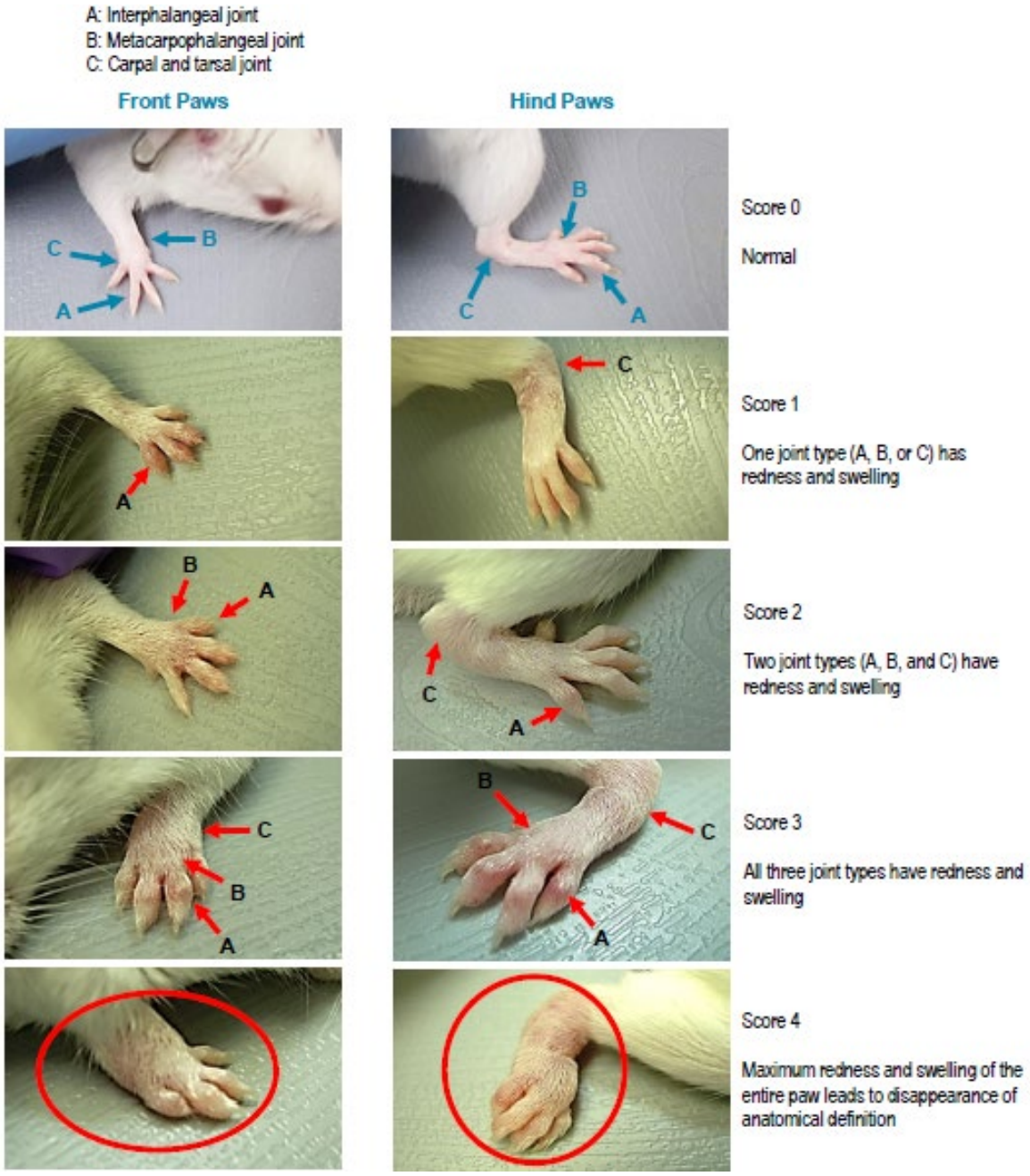
3. **Model Considerations**
   a. Refinements/supportive measures
      i. Consider a warmer housing temperature, heat support, or additional nesting material/huts
      ii. Soft nesting material that cannot become tangled (e.g. nestlets)
      iii. Soft bedding
      iv. Soft food or gel diet on cage floor for nutritional and hydration support
      v. Cupping mice during handling instead of lifting by the tail
   b. Pain
      i. Arthritis is considered to be a painful condition and should be placed into category E and justified if analgesics cannot be administered when signs of pain are observed
   c. Scoring Systems
      i. Multiple scoring systems have been described in the literature for the different arthritis models.
      ii. A scoring system should be used daily to quantifiably evaluate each animal. The protocol should clearly describe the scoring system which will be implemented. (*see attached examples*)
      iii. The protocol should describe humane endpoints associated with the scoring system used which would require the animals to be removed from study early.

Paw Scoring System (CIA)

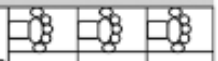
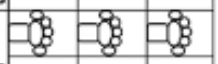
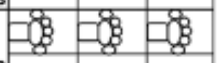
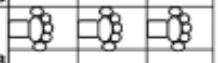
Paw score	Clinical observations
0	Normal paw. No obvious differences in appearance vs. healthy mice.
1	One or two toes inflamed and swollen. No apparent swelling of paw or ankle.
2	Three or more toes inflamed and swollen, but no paw swelling, OR Mild swelling of entire paw
3	Swelling of entire paw.
4	Severe swelling of entire paw and all toes, OR Ankylosed paw and toes and the mouse cannot grip the wire top of the cage.

https://hookelabs.com/services/cro/cia.html

Arthritis Scoring System (Adjuvant Induced)



https://www.chondrex.com/documents/Scoring-System.pdf

Experiment:					
			Baseline		
Animal ID :		**Date**			
		Day			
Behaviour (assessed in home cage prior to handling)			**Score**	**Score**	**Score**
A. Normal interactions with cage mates	0				
Reduced interest in roaming behaviour	2				
Isolated from cagemates (provide additional house)	5				
		Total Score			
Coat condition (prior to scruffing)					
Normal	0				
Lack of grooming	1				
Stary coat	2				
		Total Score			
Body weight (compared to an age-matched control)					
Weight					
Normal (within 10% of age matched control)	0				
>10 % weight loss (provide soft, palatable food)	2				
>15%	5				
		Total Score			
Mobility (assessed in a separate cage, choose best match/highest score that applies)					
B. Normal	0				
Abnormal gait (e.g shuffles)	1				
Hobbling (e.g reluctance to put full weight on all legs)	2				
Paddling with affected leg	3				
Absence of load bearing on affected leg (e.g. when standing on hind paws)	5				
Sledging (using tail to move) or absence of load bearing on both legs	10				
		Total Score			
Mouse Grimace Scale (sum all that apply)					
Orbital Tightening (+1)					
Nose Bulge (+1)					
Cheek Swelling (+1)					
Ear Position (+1)					
Whisker Change (+1)					
Hunched Posture (+3)					
Involuntary Shaking / Shivering (+5)					
Altered Breathing (+5)					
		Total Score			
Arthritic paw score (see table below)					
C. **Front Left**					
		Score out of 3			
Front Right					
		Score out of 3			
Rear Left					
		Score out of 3			
Rear Right					
		Score out of 3			
		Total Score			
Caliper measurement					
		Front Left			
		Front Right			
		Rear Left			
		Rear Right			
		Left Ankle			
		Right Ankle			
Abnormal response to caliper measurement	2				
D.		**Global score: Sum all parameters (shaded boxes only)**			

Arthritic paw score	
No swelling	0
Swelling affecting a single digit or joint	1
Localised swelling affecting multiple joints	2
Generalised swelling affecting multiple joints	3

References

- Applicability and implementation of the collagen-induced arthritis mouse model, including protocols (Review)https://www.spandidos-publications.com/10.3892/etm.2021.10371
- Applying refinement to the use of mice and rats in rheumatoid arthritis research
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- https://hookelabs.com/services/cro/cia.html
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- Collagen-induced arthritis Nature Protocols https://www.nature.com/articles/nprot.2007.173
- Bench to Bedside: Modelling Inflammatory Arthritis Discovery Immunology, 2022, 2, 1–14 https://doi.org/10.1093/discim/kyac01