刘学武,唐梓宁,彭冬冬,等. 雪貂在抗感染药物非临床研究中的应用[J]. 中国实验动物学报, 2024, 32(6): 799-818.
LIU X W, TANG Z N, PENG D D, et al. Use of ferrets in nonclinical studies of anti-infective drugs [J]. Acta Lab Anim Sci Sin, 2024, 32(6): 799-818.
Doi:10.3969/j.issn.1005-4847.2024.06.013

雪貂在抗感染药物非临床研究中的应用

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【摘要】 雪貂应用于抗感染药物评价的优势在于病原微生物(尤其是病毒株)能不经宿主适应直接进行感染和传播,且动物感染后的临床症状与人极为相似。虽然雪貂在抗病毒药物的研发中起到了极为重要的作用,但其应用范围仍有一定的局限性,可能与雪貂缺少相应的实验动物饲养和应用的国家级标准,缺乏特异性的诊断和检测试剂等因素有关。本文对雪貂作为感染疾病模型的特点进行总结,并汇总分析了雪貂在抗感染药物研究中的应用方向,旨在促进雪貂作为实验动物的标准化应用。

【关键词】 雪貂;抗感染药物;标准;实验动物
【中图分类号】Q95-33 【文献标志码】A 【文章编号】1005-4847(2024)06-0799-20

Use of ferrets in nonclinical studies of anti-infective drugs

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【**Abstract**】 Ferrets offer an advantage in nonclinical studies of anti-infective drugs because of their ability to be infected with and spread pathogenic microorganisms, especially viral strains, without the need for host adaptation. Additionally, the clinical symptoms exhibited by infected ferrets are very similar to those of humans. Although ferrets play a very important role in the research and development of antiviral drugs, the scope of their application remains limited. This may be related to the lack of corresponding national standards for laboratory animal feeding and application of ferrets as well as the lack of specific diagnostic and detection reagents. This paper summarizes the characteristics of ferrets as infectious disease models with a summary and analysis of the application direction of ferrets in anti-infective drug research. Our aim is to promote further standardization of the use of ferrets.

【**Keywords**】 ferret; anti-infective drugs; standards; laboratory animal
Conflicts of Interest: The authors declare no conflict of interest.

[基金项目]湖南省药物非临床研究科技创新创业团队(2021),湖南省重点研发计划(2023DK2006),“小荷”青年人才创新项目((2022)056)。
Funded by Scientific and Technological Innovation and Entrepreneurship Team of Pharmaceutical Non-Clinical Research in Hunan Province (2021), Hunan Province Key Research and Development Project (2020DK2003), “Xiao He” Youth Talent Innovation Project ((2022)056).
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雪貂因其解剖结构的特殊性、对病原微生物(尤其是病毒株)易感性以及感染后临床症状与人类的相似性,使其用于感染药物的评价具有天然的种属优势。大量针对病原微生物的生物学特性研究和对应的抗感染药物的评价均依靠雪貂作为模式动物,这其中以流感病毒、新型冠状病毒等抗病毒药物尤为显著。与此同时,针对雪貂的特异性试剂的开发和实验动物化进展却与雪貂的应用需求极不相符,本文对雪貂的特性和在抗感染药物中的应用进行总结,以期为雪貂的推广应用提供资料参考。

1 雪貂的生物学特性

1.1 雪貂的生理特性

雪貂是食肉目鼬科貂属的夜食性哺乳动物,天生喜静,对外界环境的刺激具有高度警惕性。因其天生缺乏汗腺[1],不适宜生存于高温环境。雪貂属于季节性发情动物,繁殖期为 5 ~ 6 年,每个季节可获得两胎幼仔。寿命 7 ~ 10 年,平均体重 0.3 ~ 2.5 kg,雌雄体重差异较大。

1.2 解剖学特性

雪貂天生缺乏汗腺和盲肠,且雄貂缺乏前列腺[1]。雪貂的气管较长,上下呼吸道分腔明显,上、下呼吸道的解剖比例、支气管壁粘膜下腺的密度和终末细支气管的代数都与人类呼吸道的情况相似[2-3],有利于研究外源性物质(如病毒、药物,尤其是吸入制剂)对呼吸道不同区域的效应/毒性差异。雪貂的食管形态学结构和分子表达与人较为相似,其中雪貂的食管粘膜下腺体与人类相似,而小鼠、大鼠或兔等均无粘膜下腺体[4-6],且雪貂食管的分子表达(如 CK1-CK20、Mucin、LEF1 等)与人较为相近,可作为人食管疾病的模型动物之一[7]。雪貂具有恶心、干呕、呕吐等呕吐反射特征,与其缺乏食道括约肌有关[1,7],较适合用于观察胃肠型病原微生物感染后的相应临床症状。

2 雪貂感染病原微生物后的组织分布情况

考察病原微生物在动物模型中的组织分布对了解病原微生物的生物学特性(包括组织嗜性、宿主危害性等)、解释宿主的反应性、提示临床重点关注部位等均具有重要意义。BELSER 等[8]在雪貂用于流感病毒感染模型的使用指南中提出,感染性标本的收集顺序应从预期病毒载量最低的组织到最高病毒载量的组织,其中呼吸道(鼻甲、气管和肺、肺泡灌洗液)、眼部(眼睛和结膜)、胃肠道、脑(重点是嗅球)的病原微生物高分布,应靠后收集。此外,在每个样本采集中间,应用 70%乙醇对解剖器械进行净化,最大限度地减少交叉污染的可能性。但需了解到的是,除病原微生物本身的组织嗜性外,其他因素(如感染途径、基因突变、免疫状态等)对其组织分布均有重要的影响,因此在设置组织采集种类和顺序时,应同时兼顾感染途径、基因突变情况和免疫状态等因素。

2.1 感染途径影响病原微生物的组织分布

经鼻或经气管滴注是研究较多的感染途径,但随着对传播途径的认识加深,研究者逐渐意识到经气溶胶传播感染和经眼部接种感染也是接近人的重要感染方式。经呼吸道途径构建雪貂感染模型后,上呼吸道是病毒或细菌高分布的部位之一,通常检测鼻冲洗液或鼻甲组织中的病毒载量来反应感染情况。KWON 等[9]的研究显示,经鼻内感染和经气管滴注感染甲型流感病毒株后,病毒在雪貂呼吸道的分布有显著性差异。其中鼻内感染途径下,流感病毒(A/broiler duck/Korea/Buan2/2014; A/breeder duck/Korea/Gochang1/2014)主要分布于鼻甲,且病毒不会向下呼吸道迁移。但采用气管滴注感染后,病毒主要分布于气管和肺,且随着感染后时间推移,病毒会进展性地分布于鼻甲。KIM 等[10]比较了乙型流感病毒在雪貂的 3 种感染途径(滴鼻感染、直接接触感染和气溶胶传播感染)。结果显示,直接滴鼻感染主要在感染早期(1 ~ 5 d)在鼻甲内有较高的病毒分布,直接接触途径则在感染后 4 ~ 7 d 内显示出鼻甲部位的病毒高分布。RIJSBERGEN 等[11]比较了 2 种感染途径下(滴鼻感染和气管滴注感染),3 型副流感病毒(human parainfluenza virus type-3, HPIV-3)在雪貂喉部的分布差异,结果显示,2 种感染途径下病毒均在喉部有较高的病毒分布,但分布时相有显著性差异。其中鼻内感染途径下,感染早期(1 ~ 7 d)在喉部有高病毒分布;气管滴注感染途径下,感染中期(3 ~ 10 d)在喉部有高病毒分布,提示感染途径影响病毒在气道内的感染性迁移。GUPTA 等[12]比较了雪貂经气管注射感染、气溶胶传播感染、接触感染(同笼饲养)3 种途径下的结核感染分布情况,结果显示,气管注射感染和气溶胶传播感染途径下,结核杆菌在

气管和肺、纵隔淋巴结、脾、肝内均有检出，且持续时间至少为 10 周以上。接触感染途径下，仅 3/6 只雪貂在鼻甲冲洗液中检出结核杆菌，1/6 只雪貂在气管中检出结核杆菌，且 2 个部位均未表现出明显的结核杆菌定植特性（即未见持续检出）。SCHIFFMAN 等[13]比较了 2 种感染途径（经鼻滴注、肌肉注射）下，线状病毒（包括埃博拉病毒（Ebola virus，EBOV））在雪貂体内的组织分布差异。结果显示，在所有感染途径下均发现了全身性病毒传播，且无论感染途径如何，在终末时间点均在肝、脾、肾和肺部发现了高病毒滴度。此外，在脑和心脏检测 EBOV、本地布焦病毒（Bundibugyo virus，BDBV）和苏丹病毒（Sudan virus，SUDV），且在所有动物中均观察到病毒从口腔、鼻腔和直肠粘膜脱落。

2.2　基因变异影响病原微生物的组织分布

病原微生物感染雪貂后，在宿主体内的分布与其变异情况有关，PULIT-PENALOZA 等[14]研究发现，雪貂感染以 1×10^6 PFU 经鼻接种严重急性呼吸综合征冠状病毒 2（severe acute respiratory syndrome coronavirus 2，SARS-CoV-2）不同亚型毒株（WA1、Alpha、Beta、Delta）后，病毒在血液和各大脏器（眼睛、结膜、软腭、鼻甲、肾、脾、肝、心脏、肠（十二指肠、空肠回肠袢和降结肠）、嗅球、脑、肺和气管）均有广泛分布，且其中以呼吸道（鼻甲（含组织和冲洗液）、软腭、支气管、肺）分布最多，此外雪貂感染不同变异株后的分布也存在明显差异，其中以 Alpha 和 Delta 病毒株的分布最为广泛。HUANG 等[15]的研究显示，雪貂经鼻感染 4 株不同来源的乙型流感病毒株（B/Brisbane/60/2008、B/Bolivia/1526/2010、两种 B/Yamagata 谱系（B/Florida/04/2006 和 B/Wisconsin/01/2010）），呼吸道组织中的病毒分布和病毒载量均有显著性差异，其中 4 株乙型流感病毒均在鼻腔中有大量复制，但其中仅 B/Brisbane/60/2008 能在下呼吸道（气管和肺）进行复制，且病毒载量也明显高于其余 3 株变异株。KIM 等[10]则通过比较乙型流感病毒野生株（B/Florida/04/06）和鼠肺适应株（经 17 代适应）经鼻滴入感染后，病毒在气道的分布情况，结果显示，经鼠肺适应后，病毒发生了显著的变异突变，表现为核苷酸和氨基酸序列的显著突变，且病毒在感染后 1 ~ 7 d 内均在鼻甲中有更高的分布，感染后 1 ~ 3 d 则在气管和肺中显示出更高的分布，提示变异能显著影响病毒的分布。

2.3　组织嗜性影响病原微生物的组织分布

组织嗜性是病原微生物（尤其是病毒）对宿主特定组织具有选择性的亲和力和致病作用的特性，是影响病毒分布的一个重要原因。病毒的组织嗜性与病毒的抗原蛋白以及宿主组织的相应结合受体的分布有关。例如与甲型流感病毒相关的是 α-2,6-唾液酸糖蛋白受体，能被甲型流感病毒的血凝素（hemagglutinin，HA）特异性识别[16]，进而进行宿主细胞的感染和致病。人和雪貂的下呼吸道（肺门的粘膜下腺体）均主要表达 α-2,6-唾液酸糖蛋白受体，因此雪貂感染后的病毒组织分布和感染症状与人极为相似。此外，雪貂上呼吸道和下呼吸道（肺门区）几乎没有 α-2,3-唾液酸受体的表达，这与人类气管组织中的相应受体表达相似。此外，占玲俊等[17]的研究发现，雪貂的支气管、肺、肾、回肠和盲肠均有唾液酸受体的典型分布，但各种亚型流感病毒株对不同组织的嗜性不完全与其受体分布一致，提示唾液酸受体并非所有流感病毒在雪貂组织中分布的决定性因子，可能还有其他因素（如其他受体或共受体等）影响到了组织病毒的组织分布。

SARS-CoV-2 主要通过靶向人血管紧张素转换酶 2（angiotensin converting enzyme Ⅱ，ACE2）受体进入宿主细胞，且 SARS-CoV-2 的 S 蛋白对 ACE2 的亲和力是 SARS-CoV 的 10 ~ 20 倍，这可能是其高传染性的原因[18]。单细胞 RNA 测序显示[19-20]，ACE2 主要表达于Ⅱ型肺泡上皮细胞（alveolar type Ⅱ cell，AT2）中，肺组织中表达 ACE2 的细胞约 83% 为 AT2 细胞，提示 SARS-CoV-2 主要感染下呼吸道。然而，除了呼吸上皮细胞外，ACE2 也在心肌细胞、肾近曲小管上皮细胞、膀胱上皮细胞以及食管、回肠和间质细胞中高表达，使得这些组织和器官允许 SARS-COV-2 感染。在系统发育上，雪貂的 ACE2 基因与人类相同，ACE2 蛋白与 SARS-CoV-2 的 S 蛋白形成 6 个氢键，产生强大的结合力，可以有效感染雪貂的上呼吸道长达 8 d，而不会引起严重疾病或死亡，所有雪貂都产生 SARS-CoV-2 特异性抗体，且雪貂受 SARS-CoV-2 感染后，主要表现出体温升高和急性细支气管炎，感染后 8 d 在鼻、唾液、尿液和粪便样本中均可检测到病毒脱落[21]。此外，CHEN 等[22]的研究显示，肌球蛋白重链 9（myosin heavy chain 9，MYH9）过表达不增强 ACE2 敲除 A549 细胞中的 SARS-CoV-2 假病毒感染，仅增加了野生型 A549 细胞中的病毒感染。但敲除 MYH9 分子显著

降低了 ACE2-A549 细胞中 SARS-CoV-2 假病毒及真病毒感染。提示 MYH9 可能是 SARS-CoV-2 对组织细胞感染的共受体,与 ACE2 共同影响了病毒在组织中的分布情况。

2.4 免疫能力影响病原微生物的分布

宿主的免疫情况对病原微生物的持续时间有直接影响,尤其是在免疫低下或免疫豁免部位,病原微生物通常能持续滞留。WATSON 等[23]的研究显示,EBOV 在肺、肝、脾、肾、睾丸、眼睛中均有大量分布,且在免疫豁免部位(眼睛、睾丸)的分布能持续更长时间,且未见明显的组织损伤,同时还存在最大程度的核酸序列突变,提示病毒在免疫豁免部位的持续残留与病毒的变异突变和宿主的免疫豁免有关。

3 雪貂感染病原微生物后的反应性

3.1 雪貂感染病原微生物的敏感性优势

多数病原微生物可不经宿主适应而直接感染雪貂,尤其是种属特异性较强的病毒(见表 1),其野生型病毒株可不经宿主适应而直接感染雪貂,并导致与人相似的临床症状,包括发热、流涕、喷嚏、咳嗽、活动减少、厌食和体重降低、感染部位的急性或慢性炎症和损伤等。啮齿类动物(如小鼠、大鼠等)通常仅存在感染后的部分症状,如小鼠感染流感病毒[24],仅存在体重降低、肺病变,无咳嗽、喷嚏、流涕、发热等症状。如帕拉米韦、玛巴洛沙韦等[25-26]神经氨酸酶抑制剂在进行抗流感病毒药效研究时,分别选用了 BALB/c 小鼠、雪貂进行不同亚型的流感病毒株(A/PR/8/34 (H1N1)、A/Kumamoto/Y5/67 (H2N2)、A/Victoria/3/75 (H3N2)、B/Maryland/1/59 or B/Lee/40 等)感染模型的构建,其中在 BALB/c 小鼠模型上进行了肺部病毒滴度、肺部病变和死亡率的考察,但在雪貂感染模型上则分别观察到了受试物对临床症状(体重、体温、喷嚏、口式呼吸、鼻部炎症反应、死亡等)的改善和鼻部病毒滴度(鼻拭子和鼻冲洗液)、肺病毒滴度的抑制作用。新冠病毒药物 regkirona 在有效性研究过程中选用了 hACE2 小鼠、仓鼠、雪貂、恒河猴进行药效研究,结果显示,regkirona 能显著降低小鼠肺病毒滴度,显著改善雪貂感染模型的临床症状(咳嗽、鼻涕、活动减少等),显著降低恒河猴鼻部和肺部病毒滴度[27]。通过比较不同种属感染模型的检测指标类型可知,小鼠主要用于观察病原学指标的变化(如病毒滴度、病毒载量),且感染部位主要集中于下呼吸道(肺部),雪貂感染模型则可同时考察病原学指标和感染后的临床症状,且感染部位可同时包括上呼吸道(鼻甲、咽喉等)和下呼吸道(肺部)。雪貂从感染部位、感染后的反应性方面均更接近于人的临床表现,因此在评价抗病毒药物相关药效时,具有明显的种属优势。

3.2 雪貂感染病原微生物的年龄相关性

有研究显示,部分病毒对雪貂的感染具有年龄特异性,例如 KIM 等[28]的研究表明,所有年龄段的雪貂均可感染 SARs-Cov-2,但老年雪貂(> 3 岁)表现出更高的病毒载量,鼻腔病毒脱落时间更长,以及更严重的肺炎症、渗出以及临床症状(与 < 6 个月的幼年雪貂和 1 ~ 2 岁的青年雪貂相比)。PRINCE 等[29]、TAYLOR 等[30]和 SUFFIN 等[31]的研究显示,呼吸道合胞病毒(respiratory syncytial virus, RSV)在所有年龄段的雪貂鼻腔组织中均有高滴度的病毒复制,但在肺中的病毒复制仅局限于幼龄雪貂,提示 RSV 对雪貂的感染特性与人类具有相似的年龄相关性。PARK 等[32]发现,发热伴血小板减少综合征静脉病毒(severe fever with thrombocytopenia syndrome phlebovirus, SFTSV)对雪貂的感染具有明显年龄依赖性,年轻成年雪貂(2 岁)没有表现出任何临床症状和死亡率,且表现出强烈的干扰素介导的抗病毒反应,而感染 SFTSV 的老年雪貂(24 岁)感染后具有更高的病毒载量,且存在持续上调的炎症免疫反应,并表现出严重的血小板减少、白细胞计数减少和高热,死亡率为 93%。多项研究显示[33-34],年龄对雪貂感染流感病毒后的反应性影响巨大,感染后的严重程度依次为老年雪貂 > 成年雪貂 > 断奶雪貂,且上述反应性差异可能与不同年龄段雪貂的气道中唾液酸糖蛋白受体的表达量具有明显的年龄差异有关,其中新断奶和老年雪貂的 α-2,6-唾液受体水平更高,以及发挥病毒清除和进展的 α-2,3-唾液酸受体则呈年龄依赖性损失[35]。雪貂作为实验动物时,虽然其使用年龄多在 6 月龄以上,但因其对多种病毒株感染的年龄依赖性特点,因此在进行抗病毒药物的研发时,应根据药物的适用人群(婴幼儿、成年人或老年人)选择合适年龄段的动物来进行研究。

3.3 雪貂感染病原微生物后的传播特点

细菌对宿主的选择性通常较弱,能感染雪貂的细菌通常也能在如大鼠、小鼠、猴等体内形成定植

和感染,但雪貂较为特有的种群传播能力(尤其是呼吸道感染后)则成为雪貂种属优势的主要原因之一[36-37],且这种感染后的传播能力可能与雪貂在感染后特有的咳嗽、喷嚏等临床症状产生了大量携带病原微生物的气溶胶有关,并最终导致气溶胶或飞沫传播[12,38]。GUPTA 等[12]的研究显示,气管内高剂量(> 5 × 10^3 CFU)结核杆菌感染雪貂,7 周内出现与大型动物如牛、猴、人等相似的急性感染期临床症状和病理特征,感染非常高剂量(> 5 × 10^4 CFU)的雪貂在 2 ~ 4 周内出现严重症状,体重降低高达 30%。急性感染时,传播更有效,会出现与封闭环境中接触活动性结核病患者类似的各种疾病症状。雪貂感染病原微生物后的反应性特点的比较见表 1。

表 1　雪貂感染病原微生物后的反应性比较

Table 1　Comparison of the reactivity of ferrets infected with pathogenic microorganisms

病原微生物 Pathogenic microorganism	感染途径 Route of infection	感染后的症状及与人的相似性 Symptoms after infection and their similarity to humans	其他动物种属模型的研究情况 Research on other animal species models	参考文献 References
甲型流感病毒/乙型流感病毒/禽流感病毒 Influenza A virus/influenza B viruses/avian influenza viruses	滴鼻/气管滴注/灌胃/直接接触/气溶胶接触 Intranasal/intratracheal instillation/intragastric/direct contact/aerosol contact	感染后的临床症与人相似,包括发热、体重降低、活动减少、鼻涕、咳嗽、死亡,病毒在呼吸道有明显复制,且存在种群间的传播感染,是流感病毒感染的首选动物种属 Clinical symptoms after infection are similar to those of humans, including fever, weight loss, decreased activity, nasal discharge, cough, and death. Virus has obvious replication in the respiratory tract, and there is interpopulation transmission of infection, which is the preferred animal species for influenza virus infection	BALB/c 小鼠、仓鼠、豚鼠、鸡、犬、猪、猴。小鼠(可见体重减低,肺炎,鼠肺适应株可引起死亡)、仓鼠、豚鼠几乎无临床症状,不适合进行传播研究;鸡对人类病毒不敏感;犬不是流感病毒的天然宿主,无传播能力;猪和猴较为合适,但成本高 BALB/c mice, hamsters, guinea pigs, chickens, dogs, pigs, monkeys. Mice (body weight loss, pneumonia and murine lung adapted strains can cause death), hamsters, guinea pigs have almost no clinical symptoms and are not suitable for transmission studies. Chickens are not sensitive to human viruses. Dogs are not the natural host of influenza virus and have no ability to transmit. Pigs and monkeys are more suitable, but the cost is high	[36-45]
呼吸道合胞病毒 Respiratory syncytial virus	滴鼻/气管滴注 Intranasal/intratracheal instillation	无明显临床症状(或仅见轻度体温升高),但存在血清细胞因子(IL-1α、IL-1β、INF-α、INF-β)的变化,存在种群间传播。在鼻腔中的病毒复制与年龄无关,但在肺部的病毒复制情况与年龄呈负相关(唯一的与人相似的动物种属) There were no obvious clinical symptoms (or only mild temperature increase), but there were changes in serum cytokines (IL-1α, IL-1β, INF-α, INF-β), and there was interpopulation transmission. Viral replication in the nasal cavity is independent of age, but in the lungs is inversely associated with age (the only animal species similar to humans)	BALB/c 小鼠、大鼠、黑猩猩、棉鼠、牛、豚鼠、仓鼠、猴 BALB/c mice, rats, chimpanzees, cotton mice, cattle, guinea pigs, hamsters, monkeys	[29-31,46-48]
SARS (SARS-Cov/SARS-Cov-2)	滴鼻/气管滴注/灌胃/直接接触/气溶胶接触 Intranasal/intratracheal instillation/intragastric/direct contact/aerosol contact	感染后存在发热、急性支气管炎,且存在种群间的传播感染。临床症状(发热、呼吸道炎症)、传播感染均与人相似,是合适的动物种属 After infection, there were fever, acute bronchitis, and inter-population transmissible infection. Clinical symptoms (fever, respiratory inflammation), transmissible infection were similar to humans, so it was a suitable animal species	hACE2 转基因小鼠、非转基因小鼠(腺相关病毒转染 hACE2)、仓鼠、猴 hACE2 transgenic mice, non-transgenic mice (adeno-associated virus transfected with hACE2), hamsters, monkeys	[18-20,49-51]

续表 1

病原微生物 Pathogenic microorganism	感染途径 Route of infection	感染后的症状及与人的相似性 Symptoms after infection and their similarity to humans	其他动物种属模型的研究情况 Research on other animal species models	参考文献 References
偏肺病毒 Human metapneumovirus	滴鼻 Intranasal	感染后无临床症状,但存在病毒复制和中和抗体的产生 There are no clinical symptoms after infection, but viral replication and neutralizing antibody production are present	BALB/c 小鼠、棉鼠、豚鼠、仓鼠、非洲绿猴 BALB/c mice, cotton mice, guinea pigs, hamsters, African green monkeys	[52-54]
麻疹病毒/犬瘟热病毒(替代病毒) Measles virus/ canine distemper virus (alternative virus)	滴鼻/气管滴注/脑内注射 Intranasal/ intratracheal instillation/ intracranial	麻疹病毒(MV):常规途径不易感,ICV 途径可见神经毒性(脑膜炎); 犬瘟热病毒(CDV):易感,感染后可见发热、咳嗽、皮疹、肺炎、神经毒性等,且感染后的临床症状与人相似,但病变更严重,疾病进展更快,不是最佳的动物种属 Measles virus (MV): Conventional route is not susceptible, ICV route can show neurotoxicity (meningitis); Canine distemper virus (CDV): susceptible, fever, cough, rash, pneumonia, neurotoxicity can be seen after infection, clinical symptoms after infection are similar to humans, but the lesions are more serious and the disease progresses faster, not the best animal species	转基因小鼠、猴(新大陆猴、松鼠猴、猕猴、食蟹猴),其中猕猴和恒河猴是所有动物(包括雪貂)中最接近人的 Transgenic mice, monkeys (New World monkeys, squirrel monkeys, macaques, crab-eating monkeys), of which macaques and rhesus monkeys are the closest to humans of all animals (including ferrets)	[55-59]
风疹病毒 Rubella virus	经胎盘/脑内注射/滴鼻/皮下注射/腹腔注射 Transplacental/ intracranial instillation/ intranasal/ subcutaneous/ intraperitoneal	感染后症状包括脑血管内皮细胞肿胀和壁变性,血管腔内积聚颗粒状嗜酸性粒细胞碎片,与风疹感染的人类胚胎相似的血管异常 Post-infection symptoms include swelling and wall degeneration of cerebral vascular endothelial cells, accumulation of granular eosinophile fragments in the vascular lumen, and vascular abnormalities similar to those seen in rubella infected human embryos	小鼠,多采用蛋白衣壳或抗原复合物进行免疫原性和候选疫苗的评价 In mice, protein capsid or antigen complex were used to evaluate immunogenicity and candidate vaccines	[21, 60-63]
丝状病毒(埃博拉病毒、马尔堡病毒、苏丹病毒、本地布焦病毒、雷斯顿病毒) Filovirus (Ebola virus, Marburg virus, Sudan virus, Bundibugyo virus, Reston virus)	滴鼻/气管滴注/肌内注射 Intranasal/ intratracheal instillation/ intramascular	无需进行宿主适应,病毒存在全身性复制,且感染后症状与人非常相似,包括体重降低、发热、皮疹、出血、凝血障碍、淋巴细胞减少、中性粒细胞增多、血小板减少、炎症反应、多器官衰竭、死亡(感染后的死亡率高于人),是非常合适的动物种属(尤其针对无宿主适应性的特征) No host adaptation is required, the virus replicates throughout the body, and the symptoms after infection are very similar to those of humans, including weight loss, fever, rash, bleeding, clotting disorders, lymphocytopenia, neutrophilia, thrombocytopenia, inflammation, multiple organ failure, and death (mortality after infection is higher than in humans). It is a very suitable animal species (especially for the characteristics of no host adaptation)	BALB/c 小鼠、C57BL/6 小鼠,ICR 小鼠,金黄地鼠、豚鼠、猴,除猴以外,其余均需进行宿主适应 BALB/c mice, C57BL/6 mice, ICR mice, golden hamsters, guinea pigs, monkeys, except monkeys, all require host adaptation	[64-68]
尼帕病毒 Nipah virus	滴鼻/直接接触/气溶胶接触 Intranasal/ direct contact/ aerosol contact	感染后具有与人相似的临床症状,包括体重降低,发热、脑炎,肺、脾和肝损伤、出血(眼眶、面部和颈部等的皮下、脑、肺、脾)、死亡、神经系统损伤(后遗症:震颤、癫痫、脑瘫等),首选的动物种属 Clinical symptoms similar to humans after infection, including weight loss, fever, encephalitis, lung, spleen, and liver damage, bleeding (subcutaneous of orbital, face, and neck, brain, lung, spleen, etc.), death, neurological damage (sequelae: tremor, epilepsy, cerebral palsy, etc.), preferred animal species	小鼠、仓鼠、猪、非洲绿猴、狨猴,小鼠神经系统无法感染病毒,基于经济、临床一致性考察,仓鼠、雪貂是理想的动物模型 Mice, hamsters, pigs, African green monkeys, marmosets, mice nervous system can not be infected with the virus, based on economic and clinical consistency, hamstersand ferrets are ideal animal models	[69-75]

续表 1

病原微生物 Pathogenic microorganism	感染途径 Route of infection	感染后的症状及与人的相似性 Symptoms after infection and their similarity to humans	其他动物种属模型的研究情况 Research on other animal species models	参考文献 References
流行性腮腺炎病毒 Mumps virus	滴鼻/气管滴注/ Intranasal/ intratracheal instillation	感染后仅见轻微临床症状，可包括体温升高（不超过 40 ℃），未见其他临床症状，病毒复制具有自限性，鼻洗液检出少量或未检出病毒（与不同亚型的临床分离株有关），口腔拭子、尿液、粪便或组织匀浆中未检测到活病毒或病毒 RNA。可产生特异性血清抗体，并产生了与感染一致的细胞因子（INF-γ、IL-2、IL-6、IL-10），不是合适动物种属 Only mild clinical symptoms are seen after infection, which may include an increase in body temperature (not exceeding 40 ℃), no other clinical symptoms, self-limited viral replication, little or no detectable virus in nasal wash (associated with clinical isolates of different subtypes), and no live virus or viral RNA detected in oral swabs, urine, feces, or tissue homogenates. It produces specific serum antibodies and produces infection-consistent cytokines (INF-γ, IL-2, IL-6, IL-10), which are not suitable animal species	BALB/c 小鼠、豚鼠、恒河猴。最佳动物模型为恒河猴，感染后 2 ~ 4 周出现典型的腮腺炎临床症状。但无发烧或神经系统症状。 BALB/c mice, guinea pigs, rhesus monkeys. Best animal model is the rhesus monkey, which presents with typical clinical symptoms of mumps 2 ~ 4 weeks after infection. But no fever or neurological symptoms.	[76-78]
副流感病毒 Parainfluenza virus	滴鼻/气管滴注/直接接触/ Intranasal/ intratracheal instillation / direct contact	成年雪貂：未见发热、体重降低等临床症状；有中和抗体产生，上、下呼吸道均存在病毒复制 幼龄雪貂：可在感染后 24 ~ 72 h 内引起动物死亡，是较合适的动物种属 Adult ferret: No fever, weight loss and other clinical symptoms; Neutralizing antibodies were produced, and virus replication existed in both upper and lower respiratory tract Juvenile ferret: can cause death within 24 ~ 72 h after infection, is a more suitable animal species	小鼠，非洲绿猴和幼龄雪貂存在感染后的临床症状，是较合适的模型 Mice, African green monkeys and young ferrets present clinical symptoms after infection, are suitable models	[79-84]
裂谷热病毒 Rift Valley fever virus	滴鼻/皮下注射 Intranasal/ subcutaneous	存在与人感染相似的临床症状，皮内或鼻内感染后，病毒能广泛分布在各大脏器，其中脾和脑中病毒载量最高。雪貂感染后出现高热、体重减轻、淋巴细胞减少和低白蛋白血、中枢神经系统疾病，表现为癫痫发作、共济失调和/或后肢无力。有短暂的病毒性 RNA 血症，脑内高病毒 RNA 载量和脑炎的组织病理学证据。是合适的模型动物之一 There are clinical symptoms similar to human infection. After intradermal or intranasal infection, the virus can be widely distributed in all major organs, with the highest viral load in the spleen and brain. Ferrets with infection develop high fever, weight loss, lymphocyopenia and low albumin blood, central nervous system disease, manifested by seizures, ataxia, and/or hind leg weakness. Histopathological evidence of transient viral RNA emia, high viral RNA load in the brain, and encephalitis. Is one of the suitable model animals	BALB/c 小鼠，大鼠，猴，叙利亚仓鼠。大鼠的发病与感染途径相关，小鼠感染后的致死性更强，仓鼠容易诱发肝炎 BALB/c mice, rats, monkeys, Syrian hamsters. Pathogenesis of rats is related to the route of infection, the lethality of mice after infection is stronger, and the hamster is easy to induce hepatitis	[85-88]
戊型肝炎病毒 Hepatitis E virus	直接接触 Direct contact	与人具有相似的病毒复制、免疫反应和临床症状，是最合适的动物种属。感染后临床症状包括转氨酶（ALT、AST）升高，急性肝损伤，血液和粪便里均可检测到病毒 With similar viral replication, immune response and clinical symptoms to humans, it is the most suitable animal species. Post-infection clinical symptoms include elevated aminotransferase (ALT, AST), acute liver injury, and virus detection in blood and stool	免疫缺陷小鼠（嵌合了人肝细胞），猴子和普通小鼠对 HEV 均不敏感，不合适 Immunodeficient mice (chimeric human hepatocytes), monkeys, and ordinary mice were insensitive to HEV and unsuitable	[89-92]

续表 1

病原微生物 Pathogenic microorganism	感染途径 Route of infection	感染后的症状及与人的相似性 Symptoms after infection and their similarity to humans	其他动物种属模型的研究情况 Research on other animal species models	参考文献 References
结核杆菌 *Mycobacterium tuberculosis*	滴鼻/直接接触/气溶胶接触 Intranasal/direct contact/aerosol contact	与人相似的感染症状、免疫反应和传播风险，感染后的临床症状包括体温升高、体重降低、接种部位的肉芽肿，肺部感染，并向各大脏器进行分布感染，体液免疫。优势在于能建立潜伏感染模型，能进行种群间的传播感染研究，是非常合适的动物种属 Symptoms of infection, immune response and transmission risk are similar to those of humans. Clinical symptoms after infection include elevated body temperature, weight loss, granuloma at the vaccination site, lung infection, and distribution of infection to major organs, and humoral immunity. Advantage is that it can establish the model of latent infection and carry out the study of transmissible infection between populations, so it is a very suitable animal species	小鼠和大鼠（不形成干酪样坏死，且无潜伏期）、豚鼠、兔（特定的高毒力致病株）、猴（容易形成大暴发，优势在于能通过免疫抑制诱导复发）、牛 Mice and rats (no caseous necrosis and no latency), guinea pigs, rabbits (specific highly virulent strains), monkeys (prone to large outbreaks, with the advantage of inducing relapse through immunosuppression), cattle	[93-102]
螺旋杆菌 *Helicobocton pyloni*	灌胃 Intragastric	雪貂是雪貂螺旋杆菌的天然宿主，主要定植于十二指肠近端和胃窦，能诱导慢性炎症和溃疡。感染雪貂螺旋杆菌后，能形成类似人类感染幽门螺旋杆菌的症状，但组织病理改变缺乏多核细胞浸润 Ferrets are the natural host of ferret *Helicobocton pyloni* (HP), which mainly colonizes the proximal duodenum and gastric antrum, and can induce chronic inflammation and ulcers. After infection with Helicobacter ferret, symptoms similar to human infection with HP can be formed, but the histopathological changes lack multinucleate cell infiltration	小鼠（不同品系之间有差异，C57BL/6 最佳）、大鼠（提前损伤胃黏膜增加定植）、豚鼠、蒙古沙鼠、猪、猫，其中蒙古沙鼠最佳 Mice (there were differences among different strains, C57BL/6 was the best), rats (early damage of gastric mucosa to increase colonization), guinea pigs, Mongolian gerbils, pigs, cats, among which Mongolian gerbils were the best	[103-110]
肺炎链球菌 *Streptococcus pneumoniae*	滴鼻 Intranasal	形成细菌-病毒共感染，细菌能增加病毒在粘膜定植，感染后能在种群间进行传播，呼吸道病毒感染能增加肺炎链球菌感染和传播，与人临床表现一致，是研究共感染和传播的合适动物种属之一 Formation of bacteria-virus co-infection, bacteria can increase the colonization of the virus in the mucosa, after infection can be transmitted between the population, respiratory virus infection can increase the infection and transmission of *Streptococcus pneumoniae*, consistent with human clinical manifestations, is one of the appropriate animal species to study co-infection and transmission	小鼠，但仅能研究细菌-病毒共感染对个体致病性，无法研究病原微生物的传播性 Mice, however, only the individual pathogenicity of bacteria-virus co-infection could be studied, and the transmissibility of pathogenic microorganisms could not be studied	[24,111-114]
金黄色葡萄球菌 *Staphylococcus aureus*	滴鼻 Intranasal	感染后可见体温升高，活动减少，肺泡实质性肺炎，死亡，组织器官菌负荷量，且与人相似具有更相似的免疫反应，但反应更剧烈，死亡率更高，是合适的动物种属之一 After infection, increased body temperature, decreased activity, alveolar parenchymatous pneumonia, death, tissue and organ bacterial load, and similar to humans with a more similar immune response, but more intense response, higher mortality, is one of the suitable animal species	小鼠、大鼠、兔等，几乎所有实验动物均可进行感染 Mice, rats, rabbits, etc, almost all experimental animals can be infected	[36,115-121]
大肠杆菌 O157:H7 *Escherichia coli* O157:H7	直接接触/灌胃 Direct contact/intragastric	肠道感染性结肠炎、腹泻、溶血性尿毒症，血尿，继发性肾小球损伤，部分动物伴有，血小板减少。溶血性尿毒素综合征和继发的肾损伤与人相似 Enteric infectious colitis, diarrhea, hemolytic uremia, hematuria, secondary glomerular injury, accompanied in some animals, thrombocytopenia. Hus syndrome and secondary renal injury are similar to those in humans	小鼠、大鼠、猴等，不同的血清型菌种影响感染情况 Mice, rats, monkeys, etc. different serotypes of bacteria affected the infection	[122-126]

4　雪貂在抗感染药物评价中的应用

在 20 世纪 30 年代偶然发现雪貂对人类流感病毒的天然易感性之后，继而被发现能模拟多种人类呼吸道病毒感染的疾病进程，包括呼吸道合胞病毒（respiratory syncytial virus，RSV）、副流感病毒（PIV）和严重急性呼吸综合征（SARS）冠状病毒等。到目前为止，雪貂已被用于人类/动物源病原微生物感染的多种方向研究[36]，包括病原微生物的致病性和发病机理、病原微生物的传播、免疫反应、抗病毒药物研发、疫苗免疫策略等[42]。此外，在《流感疫苗指南-非临床和临床模块》（European Medicines Agency，EMA）[127]等多个法规性文件中，雪貂被推荐为流感疫苗保护力评价实验的首选实验动物。采用雪貂进行非临床评价并上市的抗感染药物包括化学药物、生物制品和预防用疫苗，其中化学药物以抗流感病毒药物和抗冠状病毒为主，包括 M2 离子通道阻滞剂[128]、神经氨酸酶抑制剂[25,129-131]、血凝素抑制剂[132]、RNA 聚合酶抑制剂[26,133-139]、3CL 蛋白酶抑制剂[135,140]、白介素-1 受体拮抗剂[141]等，此外尚有多个其他候选化学药物处于临床前或临床研究阶段[142-147]。生物制品[148-160]有瑞达韦单抗（IgG 抗体），疫苗主要以流感疫苗（包括甲型流感、乙型流感和禽流感）为主，包括 arepanrix、fluenz、H5N1-medimmune、focetria、pandemrix、prepandrix、pumarix，此外还有新冠病毒疫苗 vaxzevria 等。此外，在多个丙肝病毒药物[161-162]研发过程中，基于具有与人相似的呕吐反应，雪貂还作为安全药理学实验中的试验对象，进行胃肠道系统副作用的评价[1,8,163]（见表 2）。

5　雪貂的免疫学机制研究进展

雪貂在感染性疾病（尤其是呼吸系统感染性疾病）中的应用主要集中于病原体感染后的发病机制和传播研究以及疫苗的临床前评价，但针对病原体感染后的免疫学机制研究仍进展缓慢，可能主要与以下原因有关。

5.1　雪貂的应用范围仍较局限

不同于大、小鼠等啮齿类动物，雪貂目前主要应用于感染疾病模型和呕吐模型的构建，过窄的应用范围导致对特殊试剂（如单克隆抗体、分子探针等）的需求压力较小，无法加速免疫学基础研究的进步。但需注意到的是，雪貂在其他疾病领域（包括消化系统和中枢神经系统等）的种属优势正在逐步被发掘，例如有研究发现，雪貂是幽门螺旋杆菌的天然宿主[109]，且只有雪貂和人的幽门和十二指肠的布鲁纳氏腺不含有酸性黏膜物质[1]，因此雪貂在消化系统疾病领域的优势还有较大的开发空间。此外，雪貂很容易被诱导高血氨，也能承受高血氨，是理想的氨代谢动物模型[164]。同时雪貂的脑回结构和人非常相似，是研究脑部发育的理想动物种属之一[165]。通过扩大雪貂的应用范围能加快特异性试剂的开发，促进雪貂免疫学机制研究的进展。

5.2　对雪貂的遗传信息了解较少

关于雪貂的遗传信息解密仍停留于基因组测序草图[166]，用于表征免疫反应的基因组序列信息极度缺乏，这其中就包括编码 B 细胞或 T 细胞受体的免疫特征性基因尚未得到充分的表征[167]，导致免疫细胞亚群标记物和细胞因子单克隆抗体的制备和生产受限，这些均限制了采用雪貂在免疫机制研究方面的进展。2018 年已有研究者完成雪貂的组织相容性复合体（major histocompatibility complex，MHC）测序[39-41]，2021 年 JIANG 等[168]则通过多重 PCR 法对雪貂 B 细胞受体进行测序，完成了雪貂重组单克隆抗体的制备，2018 年 LIU 等[169]则通过单细胞 PCR 法开发了小鼠抗雪貂 CXCR5 和 PD-1 单克隆抗体。这些研究成果在促进雪貂抗体试剂的开发和雪貂在免疫机制研究方面的应用作用巨大。

5.3　对雪貂的免疫系统功能了解较少

迄今为止，对雪貂的免疫系统的功能了解甚少，例如研究者已鉴定出犬和水貂等多种肉食动物的 4 种不同亚型的免疫球蛋白 G（immunoglobulin G，IgG），在猫的体内也鉴定出了 3 种亚型 IgG，这提示雪貂体内可能也存在多种亚型 IgG，但到目前为止，研究者仅在雪貂体内鉴定出 1 种 IgG 亚型，且对 Fc 受体的多样性和功能研究甚少[41]，这对研究雪貂 IgG 和 Fc 受体亚型介导的抗体效应功能（如抗体依赖型细胞介导的细胞毒性作用（antibody-dependent cell-mediated cytotoxicity，ADCC））具有限制作用。此外，目前仍无法从雪貂 B 细胞中分离出单克隆抗体，进一步限制了雪貂对流感病毒等病原体抗原蛋白识别的相关研究[169]。此外，雪貂缺乏大量的物种特异性试剂[39-41]，免疫机制研究过程中所需的免疫细胞标记物和细胞因子单克隆抗体的鉴定主要依赖于筛选与雪貂对应物发生交叉反应的其他物种的抗体[40-41,57]，这种低效的抗体筛选方

表 2 基于雪貂研究的上市抗感染药物或候选药物汇总

Table 2 Summary of marketed anti-infective drugs or candidates based on ferret studies

药物名称/受试物名称 Drug name/name of the subject	作用机制和特点 Mechanism and characteristics of action	适应症 Indication	给药途径 Route of administration	研究阶段 Research phase	雪貂的应用方向 Application direction of ferret	参考文献 References
金刚烷 Amantadine hydrochloride	M2 离子通道阻滞剂 M2 ion channel blocker	抗甲型流感病毒感染 Anti-influenza A virus infection	口服 Oral	上市 On the market	有效性/药代动力学 Main pharmacodynamics/pharmacokinetics	–
金刚乙胺 Rimantadine hydrochloride	M2 离子通道阻滞剂 M2 ion channel blocker	抗甲型流感病毒感染 Anti-influenza A virus infection	口服 Oral	上市 On the market	有效性/药代动力学 Main pharmacodynamics/pharmacokinetics	[129]
磷酸奥司他韦 Oseltamivir phosphate	神经氨酸酶抑制剂 Neuraminidase inhibitor	抗甲型流感病毒感染 Anti-influenza A virus infection	口服 Oral	上市 On the market	有效性/药代动力学 Main pharmacodynamics/pharmacokinetics	[130]
帕拉米韦 Peramivir	神经氨酸酶抑制剂 Neuraminidase inhibitor	抗甲型流感病毒感染 Anti-influenza A virus infection	静脉 Intravenous	上市 On the market	有效性/药代动力学 Main pharmacodynamics/pharmacokinetics	[25]
扎那米韦 Zanamivir	神经氨酸酶抑制剂 Neuraminidase inhibitor	抗甲型流感病毒感染 Anti-influenza A virus infection	吸入 Inhalation	上市 On the market	有效性/药代动力学 Main pharmacodynamics/pharmacokinetics	[131]
拉尼娜米韦 Laninamivir	神经氨酸酶抑制剂 Neuraminidase inhibitor	抗甲型流感病毒感染 Anti-influenza A virus infection	吸入 Inhalation	上市 On the market	有效性 Main pharmacodynamics	[131]
阿比朵尔 Arbidol	血凝素抑制剂 Hemagglutinin inhibitors	甲型和乙型流感及其他急性呼吸道病毒感染;复发性疱疹感染的联合治疗 Influenza A and B and other acute respiratory viral infections; Combination therapy for recurrent herpes infection	口服 Oral	上市 On the market	有效性 Main pharmacodynamics	[132]
法匹拉韦 Favipiravir	RNA 聚合酶抑制剂 RNA polymerase inhibitors	抗甲型流感病毒感染 Anti-influenza A virus infection	口服 Oral	上市 On the market	有效性 Main pharmacodynamics	[134]
玛巴洛沙韦 Baloxavir Marboxil	RNA 聚合酶抑制剂 RNA polymerase inhibitors	抗甲型流感病毒感染 Anti-influenza A virus infection	口服 Oral	上市 On the market	有效性/药代动力学 Main pharmacodynamics/pharmacokinetics	[26]
莫诺拉韦 Molnupiravir	RNA 聚合酶抑制剂 RNA polymerase inhibitors	抗新型冠状病毒感染 Anti-SARS-Cov-2 infection	口服 Oral	上市 On the market	有效性/药代动力学 Main pharmacodynamics/pharmacokinetics	[135]
氢溴酸氘瑞米德韦 Deuremidevir Hydrobromide	RNA 聚合酶抑制剂 RNA polymerase inhibitors	抗新型冠状病毒感染 Anti-SARS-Cov-2 infection	口服 Oral	上市 On the market	有效性 Main pharmacodynamics	[136]
瑞德西韦 Remdesivir	RNA 聚合酶抑制剂 RNA polymerase inhibitors	抗埃博拉病毒/新型冠状病毒感染 Anti-ebola virus/SARS-Cov-2 infection	口服 Oral	上市 On the market	有效性 Main pharmacodynamics	[136]
ZSP1273	RNA 聚合酶抑制剂 RNA polymerase inhibitors	抗甲型流感和禽流感病毒感染 Anti-influenza A and avian influenza virus infection	口服 Oral	临床Ⅲ期 Clinical phase Ⅲ	有效性 Main pharmacodynamics	[137]

续表 2

药物名称/受试物名称 Drug name/ name of the subject	作用机制和特点 Mechanism and characteristics of action	适应症 Indication	给药途径 Route of administration	研究阶段 Research phase	雪貂的应用方向 Application direction of ferret	参考文献 References
4'-氟尿苷 4'-Fluorouridine	RNA 聚合酶抑制剂 RNA polymerase inhibitors	抗流感病毒/新型冠状病毒感染 Anti-influenza virus/ SARS-Cov-2 infection	口服 Oral	临床前 Prelinical	有效性 Main pharmacodynamics	[138]
恩曲他滨替诺福韦 Emtricitabine Tenofovir	RNA 聚合酶抑制剂 RNA polymerase inhibitors	抗新型冠状病毒感染 Anti-SARS-Cov-2 infection	口服 Oral	临床前 Prelinical	有效性 Main pharmacodynamics	[139]
GS-621763	RNA 聚合酶抑制剂 RNA polymerase inhibitors	抗新型冠状病毒感染 Anti-SARS-Cov-2 infection	口服 Oral	临床前 Prelinical	有效性 Main pharmacodynamics	[136]
帕克洛维 Paxlovid	3CL 蛋白酶抑制剂 3C-like protease inhibito	抗新型冠状病毒感染 Anti-SARS-Cov-2 infection	口服 Oral	上市 On the market	有效性 Main pharmacodynamics	[135]
GC376	3CL 蛋白酶抑制剂 3C-like protease inhibito	抗新型冠状病毒感染 Anti-SARS-Cov-2 infection	口服 Oral	临床前 Prelinical	有效性 Main pharmacodynamics	[140]
阿那白滞素 Anakinra	白细胞介素-1 受体拮抗剂，改善感染后的临床症状 Interleukin-1 receptor antagonist to improve clinical symptoms after infection	抗新型冠状病毒感染，抑制肺部炎症 Anti-SARS-Cov-2 infection, inhibit lung inflammation	皮下 Subcutaneous	上市 On the market	有效性 Main pharmacodynamics	[141]
硫酸羟氯喹 Hydroxychloroquine sulfate	自噬抑制剂 Autophagy inhibitor	抗新型冠状病毒感染 Anti-SARS-Cov-2 infection	口服 Oral	临床前 Prelinical	有效性 Main pharmacodynamics	[142]
硫唑嘌呤 Azathioprine	免疫抑制剂 Immunity inhibitor	抗新型冠状病毒感染 Anti-SARS-Cov-2 infection	口服 Oral	临床前 Prelinical	有效性 Main pharmacodynamics	[142]
塞利尼索 Selinexor	XPO1 抑制剂 XPO1 inhibitor	抗新型冠状病毒感染 Anti-SARS-Cov-2 infection	口服 Oral	临床前 Prelinical	有效性 Main pharmacodynamics	[143]
OL-1 and OL-2	免疫调节剂 Immunomodulator	抗新型冠状病毒感染 Anti-SARS-Cov-2 infection	口服 Oral	临床前 Prelinical	有效性 Main pharmacodynamics	[144]
DAS181	唾液酸酶（融合蛋白） Neuraminidase (fusion protein)	抗流感病毒感染 Anti-influenza virus infection	口服 Oral	临床Ⅱ期 Clinical phase Ⅱ	有效性 Main pharmacodynamics	[145]
硝唑尼特 Nitazoxanide	HA 蛋白转运抑制剂 HA protein transport inhibitors	抗流感病毒感染 Anti-influenza virus infection	口服 Oral	临床Ⅲ期 Clinical phase Ⅲ	有效性 Main pharmacodynamics	[146-147]
达沙韦钠 Exviera	RNA 聚合酶抑制剂 RNA polymerase inhibitors	抗丙肝病毒感染 Anti-hepatitis C virus infection	口服 Oral	上市 On the market	安全性（安全药理） Safety (safety pharmacology)	[161]

续表 2

药物名称/受试物名称 Drug name/name of the subject	作用机制和特点 Mechanism and characteristics of action	适应症 Indication	给药途径 Route of administration	研究阶段 Research phase	雪貂的应用方向 Application direction of ferret	参考文献 References
利托那韦 Viekirax	NS3/4A 蛋白酶的抑制剂 NS3/4A protease inhibitors	抗丙肝病毒感染 Anti-hepatitis C virus infection	口服 Oral	上市 On the market	安全性(安全药理) Safety (safety pharmacology)	[162]
Arepanrix	H1N1 的单价灭活疫苗 Monovalent inactivated vaccine for H1N1	抗流感病毒感染 Anti-influenza virus infection	肌内注射 Intramuscular	上市 On the market	有效性 Main pharmacodynamics	[148]
Fluenz	三价重组蛋白疫苗 Trivalent recombinant protein vaccine	抗流感病毒感染 Anti-influenza virus infection	鼻内 Intranasal	上市 On the market	有效性/安全性(安全药理,重复给药毒性) Main pharmacodynamics/safety (safety pharmacology, repeated dose toxicity)	[149]
Fluenz tetra	四价重组蛋白疫苗 Quadrivalent recombinant protein vaccine	抗流感病毒感染 Anti-influenza virus infection	鼻内 Intranasal	上市 On the market	有效性/安全性(安全药理,重复给药毒性) Main pharmacodynamics/safety (safety pharmacology, repeated dose toxicity)	[150]
Pandemic influenza vaccine H5N1 Medimmune	H5N1 的单价减毒疫苗 Monovalent live attenuated vaccine of H5N1	抗流感病毒感染 Anti-influenza virus infection	鼻内 Intranasal	上市 On the market	有效性/安全性(安全药理,重复给药毒性) Main pharmacodynamics/safety (safety pharmacology, repeated dose toxicity)	[151]
Focetria	HA 和 NA 的三价裂解疫苗 HA and NA trivalent split vaccine	抗流感病毒感染 Anti-influenza virus infection	肌内注射 Intramuscular	上市 On the market	有效性 Main pharmacodynamics	[152]
H1N1 疫苗 Pandemrix	H1N1 的单价灭活疫苗 Monovalent inactivated vaccine for H1N1	抗流感病毒感染 Anti-influenza virus infection	肌内注射 Intramuscular	上市 On the market	有效性 Main pharmacodynamics	[153]
Pumarix	H5N1 的单价灭活疫苗 Monovalent inactivated vaccine for H5N1	抗流感病毒感染 Anti-influenza virus infection	肌内注射 Intramuscular	上市 On the market	有效性 Main pharmacodynamics	[154]
Prepandrix	H5N1 的单价灭活疫苗 Monovalent inactivated vaccine for H5N1	抗禽流感病毒感染 Anti-avian influenza virus infection	肌内注射 Intramuscular	上市 On the market	有效性 Main pharmacodynamics	[155]
Vaxzevria	刺突蛋白单价重组蛋白疫苗 Monovalent recombinant protein vaccine of spike protein	抗新型冠状病毒感染 Anti-SARS-Cov-2 infection	肌内注射 Intramuscular	上市 On the market	有效性 Main pharmacodynamics	[156]

续表 2

药物名称/受试物名称 Drug name/name of the subject	作用机制和特点 Mechanism and characteristics of action	适应症 Indication	给药途径 Route of administration	研究阶段 Research phase	雪貂的应用方向 Application direction of ferret	参考文献 References
瑞丹维单抗 Regdanvimab	单克隆抗体(刺突蛋白的受体结合域) Monoclonal antibody (receptor binding domain of spike protein)	抗新型冠状病毒感染 Anti-SARS-Cov-2 infection	静脉注射 Intravenous	上市 On the market	有效性 Main pharmacodynamics	[157,27]
MEDI8852	单克隆抗体(血凝素蛋白) Monoclonal antibody hemagglutinin)	抗流感病毒感染 Anti-influenza virus infection, oral administration	静脉注射 Intravenous	临床Ⅱ期 Clinical phase Ⅱ	有效性 Main pharmacodynamics	[158-159]
莱乃康(胎盘素) Laennec (placenta)	增强免疫 Immuno-enhancement	抗新型冠状病毒感染 Anti-SARS-Cov-2 infection	静脉注射 Intravenous	临床前 Prelinical	有效性 Main pharmacodynamics	[160]

法导致大量的抗体无法被满足,研究者仅能通过间接测量免疫基因表达(如 RT-PCR、转录组分析或寡核苷酸微阵列)来考察雪貂对病原体的免疫反应机制。

6 总结与展望

自 20 世纪初以来,雪貂一直被用作抗流感病毒研究的动物模型,随着它们对人类病毒,尤其是野生型的呼吸道病毒[170]的易感性优势日益明显,更多的病原体(如细菌、真菌等)陆续被尝试,虽然雪貂对细菌和真菌感染的种属特异性弱于病毒,但因其感染后的临床症状与人类相似[171-172],且能在个体之间进行感染性传播[13],因此雪貂作为细菌类病原微生物感染的研究仍具有一定种属优势。此外,雪貂感染性模型在表征机会性感染和不同接种途径、气溶胶传播动力学以及免疫抑制或共病背景下感染的潜力仍处于初期探索阶段[57],作为感染性疾病和感染性药物研究的工具仍具有进一步开发和应用的巨大空间。因特异性试剂(如单克隆抗体、引物等)的缺乏[40-41],雪貂在感染性疾病中的应用方向主要集中于致病机制、传播研究和抗病毒疫苗的临床前评价,较少涉及病原体感染后的免疫学机制研究。遗憾的是,雪貂在我国仍属于非标准实验动物,尚无相关的国家标准,其进一步扩大应用受限于其特异性试剂的开发和实验动物标准化。

6.1 雪貂的实验动物化进展

雪貂并非我国的本土动物,在我国的应用历史较短,21 世纪初引入我国后,其配套饲养设施、遗传质量、微生物和寄生虫学等相关的规范以及进一步的动物实验操作规范和相应的背景数据仍较为缺乏。目前仅有江苏和湖南两个省份颁布了相关的地方标准[173-176]。江苏省颁布的 DB32/T 2731—2015《实验用雪貂》包括 3 部分,环境及设施(第 1 部分)、配合饲料(第 2 部分)和遗传、微生物和寄生虫控制(第 3 部分),湖南省颁布了 DB43/T 2288—2022《实验用雪貂的饲养环境及设施规范》,可供雪貂在动物生产质量控制和实验应用方面参考,但地方标准更多的是反映实验用动物的地方特色和局部地区应用情况[177],标准中的部分内容不具有普适性,仍需通过更大范围的应用实践和验证性实验,才能提升标准中各条款内容的科学性、可靠性和权威性[177-178]。关于雪貂的国家标准,需要考虑以下 5 个方面:(1)雪貂的微生物检测项目中,必检项目过少,包括流感病毒、犬瘟热病毒均属于非必检项目,但往往这些病毒属于雪貂感染模型中研究较多的病原体,因此建议进一步优化微生物检测项目内容,以满足基本的科研需求;(2)雪貂的繁殖仅限于封闭群,虽能保持种群的基因多态性,但同样会导致动物生物学反应个体差异大的缺点,鉴于雪貂的生命周期和性成熟周期短、多胎生的生理特点,未来可考虑进一步培育具有不同生物学特性的近交系动物,以满足相应科学研究的需求;(3)已颁布的标准仅适用于普通级雪貂,不适用于 SPF 级雪貂,鉴于雪貂对多种病原微生物的易感性,建议进一步开发 SPF 级雪貂,以减少自发病对实验结果的

影响[1]；(4)标准中缺乏雪貂的实验动物管理和福利伦理相关条款，建议在逐步扩大雪貂应用范围的同时，建立符合雪貂基本伦理福利需求的审查体系[179]；(5)此外，实验操作相关的规范和标准需进一步建立，例如生物学特性数据测定、实验基本操作技术、常用感染模型的制备等[177]。

6.2 雪貂的应用前景展望

雪貂在研究多种人类感染性疾病的发病机制和传播以及疫苗的临床前评价方面具有巨大的应用价值，通过进一步的实验动物标准化和特异性试剂的开发能完善雪貂在感染性疾病领域的应用，尤其是针对新发现病原体的研究可能较其他动物种属具有更大的应用价值[22,180]。

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[收稿日期] 2023-09-20