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MESTRADO INTEGRADO EM MEDICINA

Baby got Back? In-utero Stem Cell Patches for Myelomeningocele: A Systematic Review and Meta-analysis

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Resumo

Introdução: Estudos com animais foram realizados para avaliar o benefício de adicionar células estaminais a *patches* no tratamento intrauterino do mielomeningocele. Esta revisão sistemática e meta-análise compara o efeito de *patches* com e sem células estaminais na função motora, avaliada através da escala *Sheep Locomotion Rating* (SLR), densidade de neurónios grandes e mortalidade.

Métodos: Realizámos uma revisão sistemática conforme as diretrizes PRISMA, pesquisando nas bases de dados PubMed®, Scopus® e Web of Science® até 12 de dezembro de 2023. O risco de viés foi avaliado utilizando a ferramenta do Centro de Revisão Sistemática para Experimentação Animal em Laboratório (SYRCLE) para estudos de intervenção em animais. Para a escala SLR e densidade de neurónios grandes, realizámos uma meta-análise da diferença de médias com efeitos aleatórios. Para a mortalidade, realizámos uma meta-análise de rácios de risco com efeitos aleatórios.

Resultados: Incluímos 5 estudos na revisão sistemática e 4 estudos na meta-análise, com um total de 110 animais incluídos. Todos os estudos utilizaram modelos ovinos e células estromais mesenquimais. A meta-análise destacou uma melhoria significativa na função motora com a inclusão de células estaminais nos *patches*, evidenciada por um aumento na escala SLR (diferença média 4,51; IC 95% = 0,76; 8,26; I^2 = 50%). Também se observou um aumento notável na densidade de neurónios grandes (diferença média 9,75; IC 95% = 1,63; 17,86; I^2 = 61%). O risco de mortalidade não diferiu significativamente entre os grupos (RR = 0,86; IC 95% = 0,33; 2,23; I^2 = 0%).

Conclusão: A inclusão de células estaminais nos *patches* para o tratamento intrauterino de MMC não compromete a sobrevivência fetal e aumenta a função motora e a densidade de neurónios grandes.

Palavras-chave: Mielomeningocele, espinha bífida, cirurgia fetal, terapia com células estaminais, *patch*, função motora

Abstract

Introduction: Animal studies have been conducted to assess the benefit of adding stem cells (SC) to patches in the in-utero treatment of myelomeningocele. This systematic review and meta-analysis compare the effect of patches with and without SC on motor function, assessed through the Sheep Locomotion Rating (SLR) scale, Large Neuron Density (LND), and mortality.

Methods: We performed a systematic review according to the PRISMA guidelines, searching on PubMed®, Scopus® and Web of Science® databases up to December 12th, 2023. Risk of bias was assessed using the Systematic Review Centre for Laboratory Animal Experimentation's (SYRCLE's) tool for animal interventional studies. For SLR scale and LND, we performed random-effects meta-analysis of mean differences. For mortality, we performed random-effects meta-analysis of risk ratios.

Results: We included 5 studies in our systematic review and 4 studies in our meta-analysis, with a total of up to 110 animals included. All studies used ovine models and mesenchymal stromal cells (MSCs). Meta-analysis highlighted a significant improvement in motor function with the addition of SC to the patches, evidenced by an improvement in the SLR scale scores (mean difference 4.51 (95% CI = 0,76; 8.26), I^2 = 50%). There was also a notable rise in LND (mean difference 9.75 (95% CI = 1.63; 17.86), I^2 = 61%). Mortality risks did not differ significantly between groups (RR=0,86; 95% CI = 0.33; 2.23; I^2 = 0%).

Conclusion: The addition of SC to patches in the in-utero treatment of MMC does not compromise fetal survival and increases both motor function and LND.

Keywords: Myelomeningocele, spina bifida, fetal surgery, stem cell therapy, patch, motor function

MeSH Terms:

Fetal Therapies

Meningomyelocele

Neural Tube Defects

Spinal Dysraphism

Stem Cells

Abbreviations

CI – confidence interval

ECM – extracellular matrix

LND – large neuron density

MMC – myelomeningocele

MOMS – Management of Myelomeningocele Study

MSCs – mesenchymal stromal cells

NTD – neural tube defect

P-MSCs – placental mesenchymal stromal cells

PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses

SC – stem cells

SIS-ECM – porcine small intestine submucosa-derived extracellular matrix

SLR – Sheep Locomotion Rating

SYRCLE's – Systematic Review Centre for Laboratory Animal Experimentation's

UCD – University of California, Davis

UC-MSCs – umbilical cord mesenchymal stromal cells

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Introduction

Myelomeningocele (MMC) is a congenital birth defect recognized as the most severe form of spina bifida and the predominant Neural Tube Defect (NTD), with a worldwide incidence rate of 0.8 to 1 per 1000 live births [1]. Affected infants present with an array of neurological deficits, including mobility impairments, bowel and bladder disfunction and neurological conditions like Arnold Chiari II malformations and hydrocephalus [2]. MMC is characterized by a failure in primary neurulation, resulting in the incomplete closure of the neural tube during embryonic development. This results in the extrusion of the spinal cord and its protective meningeal membranes through vertebral gaps [3]. The condition's severity is aggravated by the intrauterine environment, where the exposed neural tissue undergoes further damage due to mechanical stresses and chemical insults from exposure to amniotic fluid [4]. This is articulated through the "two-hit hypothesis," which considers an initial failure of primary neurulation followed by secondary damage to the spinal cord during in-utero fetal development [5].

Historically, the management of MMC focused predominantly on postnatal surgical interventions aimed at mitigating the complications arising from the exposed spinal cord. However, studies showed that the longer the spinal cord remained exposed, the greater the damage it endured, emphasizing the critical role early fetal surgery could have in preventing further harm to the neural tissues [6,7]. The landmark Management of Myelomeningocele Study (MOMS) randomized control trial underscored the effectiveness of treating MMC in-utero, showing marked improvements in motor function and bladder control, decreased need for ventriculoperitoneal shunting and decreased frequency in Arnold Chiari II malformations associated with fetal repair of MMC [8]. One current technique used to treat MMC involves the application of a patch onto the MMC defect. The primary goal of this technique is to create a dura matter substitute that will cover the spinal cord to prevent further neural damage as well as prevent cerebral spinal fluid leakage. Current patches come from an array of sources, ranging from biological to synthetic materials [9].

Despite the considerable progress made in prenatal care and interventions, the ability of school-aged children to walk independently remains limited, with only 29% of these children achieving the ability to walk without assistance [10]. In the quest to address these challenges, the use of stem-cells has been investigated in animal models for fetal MMC repair [11]. This systematic review and meta-analysis aims to evaluate the effectiveness of using stem cell seeded patches versus patches alone in the in-utero treatment on MMC. Particularly focusing on whether the integration of mesenchymal stromal cells (MSCs) into the patches offers a tangible improvement in motor function, large neuron density and mortality rates.

Methods

This Meta-analysis is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (**Figure 1**) [12]. No institutional ethics approval was required.

Literature Search Strategy

A systematic electronic literature search was conducted using the PubMed®, Scopus® and Web of Science® databases, including papers from inception to December 12th, 2023 (**Supplemental Table I**).

Inclusion and Exclusion Criteria

We included interventional studies detailing the placement of a patch directly over neural tissue in-utero as a strategy for repairing MMC. The study population consisted of ovines undergoing in-vivo, in-utero application of a patch with stem cells. The comparison group comprised ovines receiving only the patch without additional stem cells. Studies were excluded if the intervention occurred postnatally, if they did not specifically include the two aforementioned groups, if the animal model was not ovine, or if they were not written in English. Additionally, editorial comments, review studies, and publications lacking full-text accessibility were also excluded.

Study Selection

After duplicates removal, titles and abstracts were screened independently for eligibility by two independent reviewers. Any disagreements were resolved through discussion between the two authors. The full text of the selected studies was then assessed for inclusion by two independent reviewers.

Data Extraction

Extracted data included author name, year of publication, type of animal model and number of animals in the control and experimental groups. Treatment information included patch material, source and type of stem cells, and defect creation method. Extracted outcomes were postnatal motor function measured via the Sheep Locomotor Rating scale (SLR), histological analysis of large neuron density (LND), and mortality. The SLR scale is a standardized rating scale developed to assess the neurologic motor function of sheep by ranking them in 7 categories of locomotor recovery [13]. Large neurons, which are characterized by having a diameter of 30-70 micrometers, a discernable nucleus, and are found in the ventral gray matter of the spinal cord, are classified as motor neurons. It is believed that an increase in LND means a reduced neuronal loss during gestation and might be responsible for functional improvements observed [14]. LND can be calculated by dividing the average number of neurons by the total cross-sectional area of gray matter, to normalize for variability in the volume of gray matter present [11]. To ensure accuracy and prevent duplicate counting of animals, all papers related to the same study were reviewed and the methods sections were examined to determine instances where animal groups were referred to as historical cohorts from previous studies. Whenever uncertainties arose, we reached out to the authors for clarification.

Quality Appraisal

Risk of bias was assessed using the Systematic Review Centre for Laboratory Animal Experimentation's (SYRCLE's) tool for animal interventional studies [15].

Data Synthesis and Statistical Methods

SLR scale and LND were presented as mean (± standard deviation). Mortality was presented using absolute and relative frequencies. For SLR scale and LND, we performed random-effects meta-analysis of mean differences. For mortality, we performed random-effects meta-analysis of risk ratios. We used the restricted maximum likelihood approach to estimate between-study variance. Heterogeneity was assessed by estimating the Q-Cochran test *p*-value and the I^2 statistic. An I^2 of >50% and a Q-Cochran test *p*-value <0.1 were deemed to represent substantial heterogeneity.

Results

Study Selection

The search strategy produced a total of 515 papers published from inception until December 2023. After duplicates removal, the title and abstracts of the remaining 376 papers were screened by two authors independently. A total of 21 papers were reviewed as full-text, and 1 paper could not be retrieved. One additional paper was identified by cross-reference searching [16]. A total of 8 papers were included in the systematic review [11,14,16-21] and 7 were included in the meta-analysis [11,14,16,18-21], as one of the papers had only one animal in the control group and hence was not able to be included in the meta-analysis. Of the 8 papers included, 4 belonged to the same study [14,18-20], yielding a total of 5 studies in the systematic review and 4 studies in the meta-analysis.

Risk of Bias Assessment

Risk of bias of the included studies is shown in **Figure 2** and **Figure 3**.

Study Characteristics

The characteristics of the eight papers included are summarized in **Table I**. The studies were conducted between 2015 and 2023 in the United States of America and France. Each study followed a consistent methodology of surgically inducing a MMC defect in an ovine model between 75 and 78 days of gestation. The defect was then repaired in utero using either a patch alone or a patch seeded with stem cells. The animals were delivered between 140 and 146 days of gestation, either through vaginal birth or cesarean section. Despite the general consistency, there were minor variations across the studies regarding the timing of the defect correction and the timing of euthanasia. Notably, while most studies performed the defect correction approximately 25 days after its creation, two studies by Guilbaud et al. and Athiel et al. deviated from this pattern by performing the MMC repair approximately 15 days post defect creation. In most studies, animals had their motor functions assessed using the SLR scale at 2 and 24 hours post-delivery, and then underwent a histopathological examination of LND post-euthanasia at one day old. However, Guilbaud's group conducted euthanasia at 2 hours post-birth, permitting only a single assessment of motor function at 1h post-birth. In one study by Wang et al., an Oasis collagen patch and human placental mesenchymal stromal cells (P-MSCs) were utilized as the patch material and stem cell source respectively, with six ovines in each group [11]. Another study by Brown et al. used fetal membranes as the patch material and human P-MSCs as the stem cell source, with one ovine in the control group and two in the experimental group. Due to having only one animal in the control group, this study could not be included in the meta-analysis for SLR, LND and mortality [17]. Notably, four studies conducted by a group at University of California, Davis (UCD) between 2017-2022, some employing the same ovine models across experiments, were combined in this meta-analysis to prevent duplicate counting of animals. This yielded 10 animals in the control group and 44 animals in the experimental group, all of which underwent motor function analysis through the SLR scale, though only 38 animals in the experimental group underwent histological examination of LND. The patch utilized in this study was a porcine small intestine submucosa-derived extracellular matrix (SIS-ECM), and the stem cells employed were human P-MSCs [14,18-20]. Finally, two additional studies conducted in France by Guilbaud et al., involving 6 animals in each group, and Athiel et al., with 4 animals in the control group and 5 animals in the experimental group, utilized fibrin patches and ovine umbilical cord mesenchymal stromal cells (UC-MSCs) [16,21]. Combining all the studies yielded a total of 61 animals in the experimental group and 26 animals in the control group for the meta-analysis of motor function assessment using the SLR scale. Additionally, there are 55 animals in the experimental group and 26 in the control group for the meta-analysis of LND. For 6 animals it was not possible to extract histological results of LND.

Synthesis of Results

A total of 8 reports from 5 studies evaluated the effects of integrating stem cells into the patch on motor function, LND and mortality. Results for these outcomes are described in **Tables II-IV**. Motor function was assessed using the SLR scale, and LND was evaluated through histopathological analysis. Meta-analysis of the SLR scale scores was possible in four of these studies, assessing a total of 61 animals in the experimental group and 26 animals in the control group. The aggregated results highlighted a significant improvement in motor function with the addition of stem cells compared to using the patch alone, as evidenced by an improvement in the SLR scale scores (mean difference 4.51 (95% confidence interval [CI] = 0,76; 8.26), I^2 = 50%) (**Figure 4**). Meta-analysis of LND was also conducted for the same four studies, assessing a total of 55 animals in the experimental group and 26 animals in the control group. The combined findings demonstrated that the inclusion of stem cells in the patch led to an increase in LND when compared to the patch alone (mean difference 9.75 (95% CI = 1.63; 17.86), I^2 = 61%) (**Figure 5**). Lastly, meta-analysis was conducted for mortality, with a total of 74 animals in the experimental group and 36 animals in the control group. Mortality was assessed for deaths that occurred only after the implementation of either the patch alone or of a patch seeded with stem cells. There was a total of 12 deaths (16.2%) in the experimental group and a total of 8 deaths (22.2%) in the control group. We found no difference in the mortality risk when comparing the use of patches seeded with stem cells versus patches alone (RR=0,86; 95% CI = 0.33; 2.23; I^2 = 0%) (**Figure 6**).

Discussion

MMC is a condition associated with high morbimortality, and further research is essential to enhance the outcomes of current in-utero interventions aimed at treating this incapacitating disease. The use of stem cells in the prenatal repair of MMC offers a revolutionary approach to further mitigating the post-natal limitations associated with this condition.

This review presents a systematic review of five studies, with four of them undergoing meta-analysis. Our objective was to compare the efficacy of conventional patches in repairing MCC with the effects observed when stem cells are incorporated into these patches. We assessed their influence on motor function through the SLR scale, LND through histopathological analysis, and mortality. The effect of adding stem cells to the patches did not increase the risk of mortality. These results suggest that the intervention did not compromise fetal survival. As for motor function and LND, the inclusion of stem cells in the patches yielded a positive outcome. An improvement in SLR scale scores indicates an enhanced motor function in the ovine model within the first 24h of birth. Whereas an increase in LND translates an increase in motor neurons. It is postulated that an increase in LND signifies a decrease in neuronal death and hence contributes to the improved motor function observed [20].

In this study we chose to limit our population to the ovine model, to assess a homogeneous population and obtain more comparable results. The ovine model is the standard large animal model used to investigate in-utero repair of MMC. Its gestational time frame allows for defect creation and repair, and its size facilitates easier manipulation during surgery [22].

All studies included in this systematic review used MSCs as the stem cell source. Three of the studies used human P-MSCs [11,14,17-20], whereas two other studies used ovine UC-MSCs [16,21]. The prenatal period is the ideal timeframe for the introduction of stem cells, as the fetal immune system is naïve and receptive to the effects of the transplanted stem cells [23,24]. This tolerance is evidenced by the absence of graft-versus-host reaction in studies using human PMSCs in ovine models. This likely results from the immunomodulatory properties of MSCs and the immature nature of the fetal immune system [25,26]. MSCs are also a good source of stem cells due to their ease of procurement. P-MSCs can be harvested from discarded placentas or chorionic villus sampling, and posteriorly expanded in a suitable timeframe [27]. As for UC-MSCs, they also possess great expansion potential, and their procurement is facilitated due to the existence of umbilical cord banks [21].

MSCs have been shown to positively influence the neurological recovery process. P-MSCs cells can produce trophic factors such as brain-derived neurotrophic factor (BDNF) and hepatocyte growth factor (HGF), which contribute to a neuroprotective effect and wound healing in the spinal repair process [11]. Additionally, they have shown anti-apoptotic effects both in-vitro and in-vivo, which translates to a reduction in cell death [28]. Through their immunomodulatory and neuroprotective effects, MSCs have been demonstrated to increase LND and improve motor outcomes in the ovine model, making them an ideal candidate for the in-utero treatment of MMC.

One concern with using stem cells is the potential for tumor formation, however multiple studies have shown that MSCs are safe to use and do not lead to any abnormal tissue growth [16,29,30]. A recent meta-analysis of the use of MSCs in humans also concluded that these cells exhibit a favorable safety profile [31]. These findings provide reassurance that the procedures validated in the ovine model could be safely applicable to human fetuses.

Our study presents several limitations. Primarily, there is a scarcity of data on stem cell-embedded patches for in-utero MMC repair. The recent nature of this field likely explains the limited body of research currently available. Aditionally, a notable limitation is that these studies use animal models, and their results might not translate to humans. Five of the papers included in our analysis have an increased risk of bias, particularly concerning allocation concealment. Finally, our literature search was confined to English-language publications, potentially excluding relevant studies published in other languages.

A further limitation arises from the necessity to combine stem cells of varying densities and maturities to allow for meta-analysis of all animals, which might obscure specific effects of different stem cell characteristics on the outcomes. Several papers within this meta-analysis delve deeper into the impact of varying ages and densities of stem cells, exploring how these factors influence the effectiveness of the outcomes measured.

Inconsistencies among the studies include variations in the source of stem cells and the timing of defect repair. Specifically, two studies, by Guilbaud et al. and Athiel et al., used a different stem cell source and conducted repairs 15 days post-defect creation, diverging from the majority that performed repairs at 25 days. Additionally, there was variation in the measurement of the SLR scale; Guilbaud's team recorded measurements only within the first hour post-birth, in contrast to other studies that monitored up to 24 hours. These discrepancies add another layer of variation that may affect comparative analysis.

There is a pressing need for further research involving larger populations of animals to investigate the effectiveness of stem cell-embedded patches designed to cover spinal tissue in the prenatal management of MMC. Future studies should focus on determining how these treatments can significantly reduce morbidity, and further clarifying in what ways are stem cells contributing to enhanced results. The ultimate aim is to translate these promising findings to human clinical applications, which could substantially alter the prognosis for MMC in humans.

In the realm of human clinical trials, a groundbreaking step has been taken with the initiation of the Cellular Therapy for In Utero Repair of Myelomeningocele (CuRe) Trial at UCD, led by Dr. Diana Farmer [32]. This pioneering human trial is the first of its kind and is expected to provide crucial insights that could lead to significant improvements in the treatment of MMC. The outcomes of this trial are eagerly anticipated, as they will play a pivotal role in shaping future therapeutic approaches in this evolving field.

Appendix

Table I. Characteristics of included studies

Study	Animal Model	No. of animals in experimental group	No. of animals in control group	Patch Material	Type of stem cell	Defect creation method	Outcomes Extracted
Wang, 2015 [11]	Ovine	6	6	Oasis collagen ECM	Human P-MSCs	Surgical creation	SLR scale score, LND, mortality
Brown, 2016 [17]	Ovine	2	1	Fetal membranes	Human P-MSCs	Surgical creation	SLR scale score, LND, mortality
UCD, 2017-22 [14,18-20]	Ovine	44 SLR 38 LND	10	SIS-ECM	Human P-MSCs	Surgical creation	SLR scale score, LND, mortality
Guilbaud, 2022 [16]	Ovine	6	6	Fibrin patch	Ovine UC-MSCs	Surgical creation	SLR scale score, LND, mortality
Athiel, 2024 [21]	Ovine	5	4	Fibrin patch	Ovine UC-MSCs	Surgical creation	SLR scale score, LND, mortality

ECM, extracellular matrix; LND, large neuron density; P-MSCs, placental mesenchymal stromal cells; SIS-ECM, porcine small intestine submucosa-derived extracellular matrix; SLR, Sheep Locomotion Rating; UCD, University of California, Davis; UC-MSCs, umbilical cord mesenchymal stromal cells.

Table II. Results for Sheep Locomotion Rating scale

Study	Experimental group		Control group	
	Number	Mean (SD)	Number	Mean (SD)
Wang, 2015 [11]	6	11.0 (4.1)	6	4.3 (2.3)
UCD 2017-2022 [14,18-20]	44	12.6 (3.6)	10	8.5 (4.7)
UCD 2019 [14]				
SC low density	8	12.4 (4.2)	-	-
SC medium density	6	12.7 (4.3)	-	-
UCD 2020 [19]				
Patch only	-	-	10	8.5 (4.7)
SC Line A	6	13.5 (2.8)	-	-
SC Line B	7	12.6 (3.5)	-	-
SC Line C	5	11.5 (4.8)	-	-
UCD 2022 [20]				
SC Clinical	12	12.9 (2.9)	-	-
Guilbaud 2022 [16]	6	3.0 (2.8)	6	0.8 (0.8)
Athiel 2024 [21]	5	14.0 (1.0)	4	6.8 (5.0)

SC, stem cells; SD, standard deviation; UCD, University of California, Davis.

Table III. Results for Large Neuron Density

Study	Experimental group		Control group	
	Number	Mean (SD)	Number	Mean (SD)
Wang, 2015 [11]	6	9.5 (4.2)	6	3.4 (3.1)
UCD 2017-2022 [14,18-20]	38	19.1 (11.6)	10	8.5 (8.6)
UCD 2019 [14]				
SC low density	8	18.9 (12.2)	-	-
UCD 2020 [19]				
Patch only	-	-	10	8.5 (4.6)
SC Line A	6	24.6 (7.3)	-	-
SC Line B	7	23.0 (15.4)	-	-
SC Line C	5	21.1 (8.8)	-	-
UCD 2022 [20]				
SC Clinical	12	13.5 (10.7)	-	-
Guilbaud 2022 [16]	6	21.6 (9.9)	6	2.3 (4.8)
Athiel 2024 [21]	5	14.4 (2.9)	4	6.5 (1.8)

SC, stem cells; SD, standard deviation; UCD, University of California, Davis.

Table IV. Results for Mortality

Study	Experimental group		Control group	
	Total No.	No. of Deaths	Total No.	No. of Deaths
Wang, 2015 [11]	6	0	6	0
UCD 2017-2022 [14, 18-20]	51	6	15	3
UCD 2017 [18]	11	3	9	3
UCD 2019 [14]				
Patch only	-	-	4	0
SC medium density	7	1	-	-
SC high density	8	2	-	-
UCD 2020 [19]				
Patch only	-	-	2	0
SC Line A	1	0	-	-
SC Line B	7	0	-	-
SC Line C	5	0	-	-
UCD 2022 [20]				
SC Clinical	12	0	-	-
Guilbaud 2022 [16]	10	4	10	4
Athiel 2024 [21]	7	2	5	1

SC, stem cells; UCD, University of California, Davis.

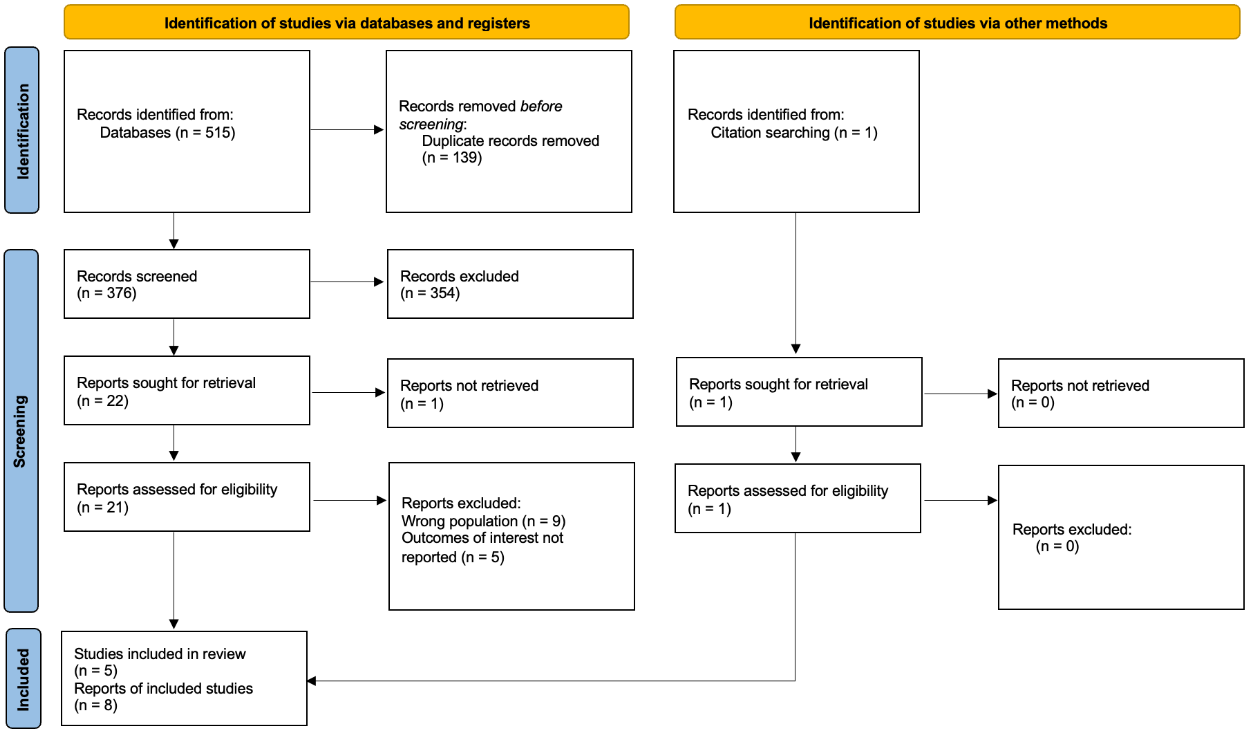

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for the selection of studies included in our analysis.

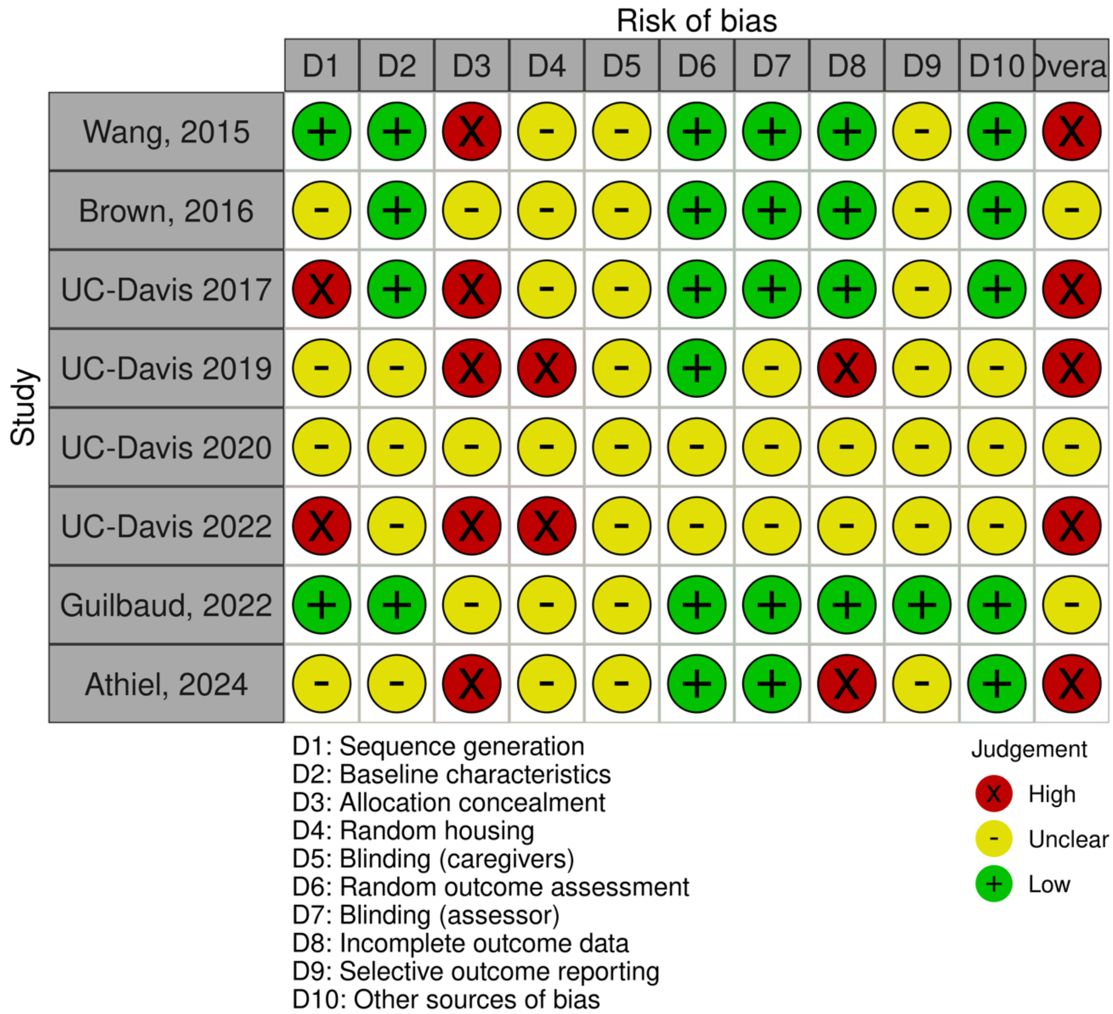

Figure 2. Risk of Bias summary

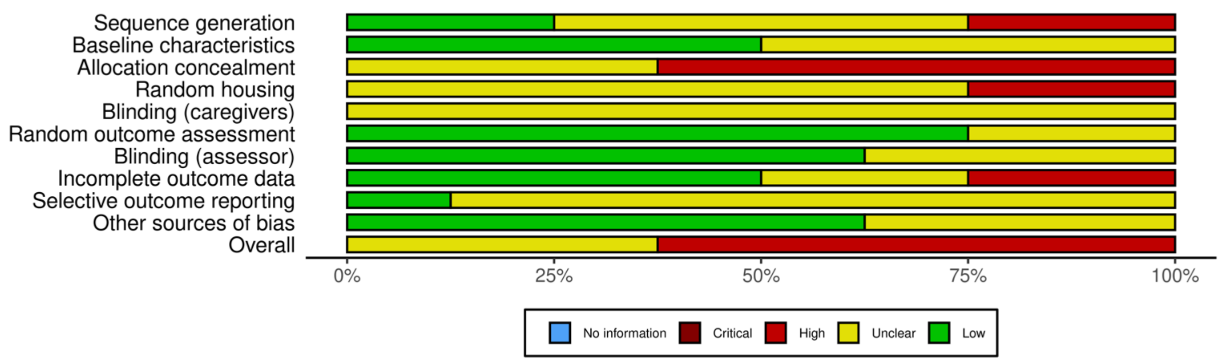

Figure 3. Risk of Bias graph

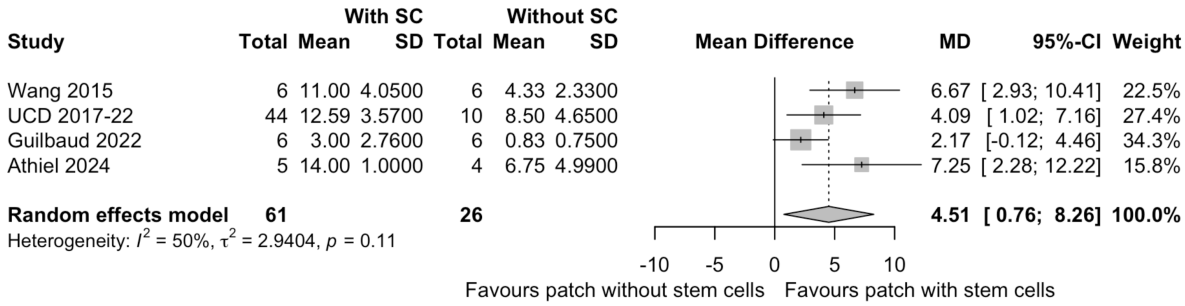

Figure 4. Forrest plot summarizing the meta-analytical results of the Sheep Locomotion Rating scale scores on the comparison between patches with stem cells *versus* patches without stem cells

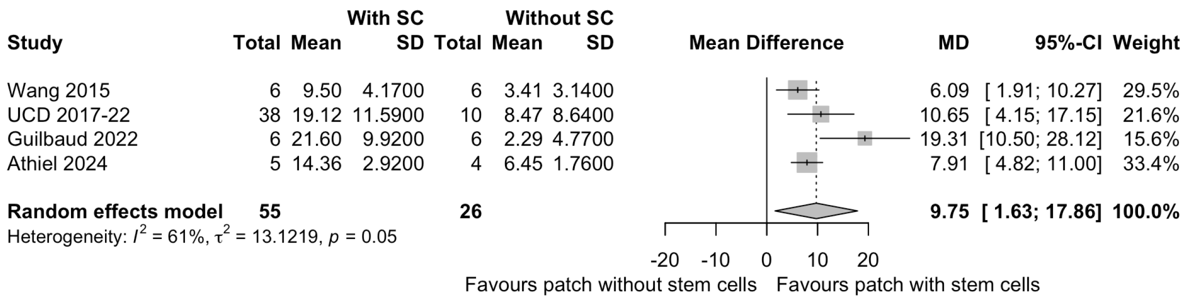

Figure 5. Forrest plot summarizing the meta-analytical results of the Lage Neuron Density on the comparison between patches with stem cells *versus* patches without stem cells

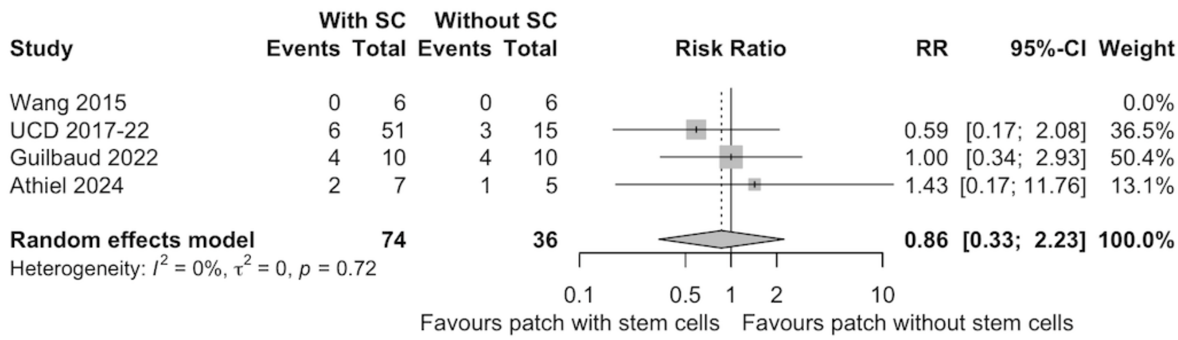

Figure 6. Forrest plot summarizing the meta-analytical results of the mortality data on the comparison between patches with stem cells *versus* patches without stem cells

Supplemental Table I. Queries applied in the different bibliographic databases

MEDLINE (Ovid)	1 exp animals/ 2 exp animal experimentation/ or exp animal experiment/ 3 exp models animal/ 4 nonhuman/ 5 exp vertebrate/ or exp vertebrates/ 6 or/1-5 7 exp humans/ 8 exp human experimentation/ or exp human experiment/ 9 or/7-8 10 6 not 9 11 exp Meningomyelocele/ 12 exp Meningocele/ 13 exp Spinal Dysraphism/ 14 exp Arnold-Chiari Malformation/ 15 Neural Tube Defects/ 16 (myelomeningocele or meningomyelocele or meningocele).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word] 17 (spinal dysraphism$ or spina bifida).mp. 18 (arnold-chiari or chiari).mp. 19 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 20 exp stem Cells/ 21 exp Cell Therapy/ 22 exp Stem Cell Transplantation/ 23 stem.mp. 24 patch$.mp. 25 20 or 21 or 22 or 23 or 24 26 19 and 25 27 10 and 26
Web of Science	1: TS=(rat OR rats OR animal OR animals OR mice OR "in vivo" OR mouse OR rabbit OR rabbits OR murine OR pig OR pigs OR dog OR dogs OR bovine OR fish OR vertebrate OR vertebrates OR cat OR cats OR rodent OR rodents OR mammal OR mammals OR chicken OR chickens OR monkey OR monkeys OR sheep OR canine OR canines OR porcine OR cattle OR bird OR birds OR hamster OR hamsters OR primate OR primates OR cow OR cows OR chick OR horse OR horses OR avian OR avians OR calf OR swine OR swines OR xenopus OR turkeys OR bear OR bears OR frog OR frogs OR zebrafish OR goat OR goats OR equine OR calves OR poultry OR macaque OR macaques OR mole OR moles OR ovine OR lamb OR lambs OR fishes OR diptera OR amphibian OR amphibians OR snake OR snakes OR ruminant OR ruminants OR hen OR hens OR piglet OR piglets OR feline OR felines OR simian OR simians OR laevis OR trout OR trouts OR teleost OR teleosts OR salmon OR salmons OR seal OR seals OR bull

	OR bulls OR ewe OR ewes OR hedgehog OR hedgehogs OR macaca OR macacas OR proteus OR pigeon OR pigeons OR bat OR bats OR duck OR ducks OR chimpanzee OR chimpanzees OR baboon OR baboons OR deer OR rana OR ranas OR carp OR carps OR heifer OR swallow OR swallows OR lizard OR lizards OR canis OR sow OR sows OR cynomolgus OR quail OR quails OR reptile OR reptiles OR turtle OR turtles OR buffalo OR gerbil OR gerbils OR boar OR boars OR squirrel OR squirrels OR oncorhynchus OR mus OR toad OR toads OR fowl OR fowls OR rerio OR danio OR ara OR aras OR musculus OR tadpole OR tadpoles OR mulatta OR salmo OR ram OR eagle OR eagles OR ferret OR ferrets OR goldfish OR catfish OR whale OR whales OR fox OR foxes OR ape OR apes OR elephant OR elephants OR bos OR marmoset OR marmosets OR cod OR cods OR shark OR sharks OR wolf OR eel OR eels OR auratus OR rattus OR zebra OR zebras OR tilapia OR tilapias OR gilt OR camel OR camels OR squid OR gallus OR marsupial OR marsupials OR vole OR voles OR fascicularis OR ovis OR salmonid OR salmonids OR tiger OR tigers OR dolphin OR dolphins OR robin OR robins OR carpio OR opossum OR opossums OR cyprinus OR salamander OR salamanders OR felis OR mink OR minks OR swan OR swans OR norvegicus OR bufo OR torpedo OR bass OR lamprey OR lampreys OR sus OR python OR pythons OR tetrapod OR tetrapods OR shrew OR shrews OR lion OR lions OR hog OR hogs OR songbird OR songbirds OR oreochromis OR starling OR starlings OR caprine OR carassius OR owl OR owls OR newt OR newts OR papio OR scrofa OR hare OR hares OR gorilla OR gorillas OR flounder OR flounders OR goose OR herring OR herrings OR therian OR buffaloes OR canary OR sparrow OR sparrows OR microtus OR octopus OR troglodytes OR tuna OR amphibia OR chinchilla OR chinchillas OR ide OR oryzias OR cervus OR kangaroo OR kangaroos OR armadillo OR armadillos OR callithrix OR "pan troglodytes" OR saimiri OR cichlid OR cichlids OR donkey OR donkeys OR bream OR char OR chars OR finch OR raccoon OR raccoons OR bothrops OR anguilla OR perch OR cricetus OR seabird OR seabirds OR buck OR bucks OR naja OR coturnix OR salmonids OR geese OR minnow OR minnows OR raptor OR raptors OR merione OR meriones OR rodentia OR elaphus OR amniote OR amniotes OR elasmobranch OR emu OR emus OR peromyscus OR hominid OR hominids OR bubalus OR crotalus OR gull OR gulls OR anas OR anura OR lemur OR lemurs OR crow OR crows OR camelus OR gibbon OR gibbons OR waterfowl OR parrot OR parrots OR eels OR cob OR stickleback OR sticklebacks OR columba OR mesocricetus OR ambystoma OR raven OR ravens OR gadus OR penguin OR penguins OR orangutan OR orangutans OR sturgeon OR sturgeons OR cuniculus OR aves OR virginianus OR cephalopod OR cephalopods OR cebus OR sparus OR tortoise OR tortoises OR guttata OR morhua OR unguiculatus OR dogfish OR vulpes OR mallard OR mallards OR apodemus OR alligator OR alligators OR oryctolagus OR llama OR llamas OR reindeer OR mustela OR duckling OR ducklings OR wolves OR sander OR amazona OR zebu OR badger OR badgers OR dove OR doves OR ictalurus OR capra OR capras OR equus OR camelid OR camelids OR poecilia OR mule OR mules OR perciformes OR salvelinus OR labrax OR cyprinidae OR ariidae OR crocodile OR crocodiles OR fundulus OR dicentrarchus OR clarias OR cercopithecus OR chiroptera OR alpaca OR alpacas OR pike OR pikes OR paralichthys OR puma OR pumas OR didelphis OR pisces OR macropus OR triturus OR bison OR bisons OR epinephelus OR gasterosteus OR panthera OR acipenser OR mackerel OR mackerels OR tamarin OR tamarins OR ostrich OR anolis OR vervet OR vervets OR wallaby OR glareolus OR beaver OR beavers OR dromedary OR catus OR killifish OR pimephales OR promelas OR aotus OR phoca OR panda OR pandas OR porpoise OR porpoises OR myotis OR yak OR yaks OR agkistrodon OR

	vipera OR otter OR otters OR turbot OR turbots OR squamate OR carnivora OR mullet OR mullets OR hawk OR hawks OR taeniopygia OR seahorse OR seahorses OR "poecilia reticulata" OR falcon OR falcons OR prosimian OR prosimians OR parus OR perca OR fingerling OR fingerlings OR antelope OR antelopes OR tupaia OR passeriformes OR sepia OR saguinus OR coyote OR coyotes OR pongo OR meleagris OR reptilia OR lepus OR psittacine OR hagfish OR warbler OR warblers OR "russell s viper" OR "russell s vipers" OR smolt OR smolts OR budgerigar OR sardine OR sardines OR cavia OR cavias OR hyla OR pleurodeles OR siluriformes OR "great tit" OR "great tits" OR guppy OR bonobo OR bonobos OR rutilus OR trichosurus OR muridae OR phodopus OR channa OR squalus OR lynx OR sturnus OR petromyzon OR vitulina OR monodelphis OR cuttlefish OR adder OR adders OR lepomis OR canaria OR gambusia OR guppies OR xiphophorus OR flatfish OR koala OR koalas OR labeo OR stingray OR stingrays OR chelonia OR lampetra OR spermophilus OR crocodilian OR "passer domesticus" OR sciurus OR artiodactyla OR ranidae OR corvus OR necturus OR platypus OR canaries OR bovid OR lagopus OR trimeresurus OR gariepinus OR marten OR martens OR drosophilidae OR mugil OR sunfish OR porcellus OR cypriniformes OR alouatta OR scophthalmus OR anser OR electrophorus OR putorius OR iguana OR iguanas OR lama OR lamas OR takifugu OR circus OR eptesicus OR flycatcher OR galago OR galagos OR trachemys OR lungfish OR characiformes OR shorebird OR shorebirds OR giraffe OR giraffes OR micropterus OR scyliorhinus OR cichlidae OR loligo OR porcupine OR porcupines OR chub OR chubs OR solea OR pleuronectes OR hylidae OR viperidae OR echis OR sorex OR anchovy OR lagomorph OR ostriches OR vulture OR vultures OR whitefish OR araneus OR jird OR jirds OR tern OR esox OR drake OR drakes OR elapidae OR gallopavo OR chordata OR myodes OR caretta OR serinus OR grouse OR misgurnus OR meles OR blackbird OR blackbirds OR coregonus OR bobwhite OR bobwhites OR heteropneustes OR mammoth OR mammoths OR turdus OR rhinella OR ateles OR characidae OR clupea OR bungarus OR brill OR "struthio camelus" OR sloth OR sloths OR pteropus OR sculpin OR anthropoids OR pollock OR pollocks OR morone OR "pan paniscus" OR litoria OR chipmunk OR chipmunks OR balaenoptera OR marmota OR melopsittacus OR hyrax OR lemming OR lemmings OR halibut OR hylobates OR lates OR caiman OR caimans OR sigmodon OR stenella OR barbel OR barbels OR sterna OR parakeet OR parakeets OR phocoena OR leptodactylus OR canidae OR buteo OR harengus OR gopher OR gophers OR marmot OR marmots OR gosling OR goslings OR platichthys OR gar OR gars OR sebastes OR marsupialia OR notophthalmus OR gazelle OR gazelles OR insectivora OR paridae OR felidae OR russula OR galliformes OR bombina OR colobus OR echidna OR echidnas OR seabass OR syncerus OR plaice OR "blue tit" OR "blue tits" OR pagrus OR catfishes OR cetacea OR barbus OR cygnus OR ficedula OR chamois OR colubridae OR perches OR coelacanth OR fitch OR urodela OR cynops OR martes OR halichoerus OR aix OR salmonidae OR leuciscus OR magpie OR magpies OR silurus OR whiting OR whitings OR anseriformes OR colinus OR rhea OR chlorocebus OR octodon OR acinonyx OR mouflon OR mouflons OR ibex OR tetraodon OR bufonidae OR equidae OR jackal OR cephalopoda OR dendroaspis OR glama OR muskrat OR muskrats OR sable OR sables OR wildebeest OR streptopelia OR albifrons OR vespertilionidae OR woodpecker OR woodpeckers OR muntjac OR muntjacs OR archosaur OR branta OR cricetulus OR megalobrama OR poeciliidae OR desmodus OR snakehead OR snakeheads OR tench OR teal OR teals OR bandicoot OR bandicoots OR apteronotus OR phyllostomidae OR crocidura OR buzzard OR buzzards OR larimichthys OR cercocebus OR

	pipistrellus OR erithacus OR impala OR impalas OR rousettus OR haddock OR haddocks OR tinca OR ratite OR calidris OR cynoglossus OR hypophthalmichthys OR bullock OR bullocks OR dromedaries OR alectoris OR filly OR salamandra OR cingulata OR bitis OR grus OR ammodytes OR macaw OR macaws OR hypoleuca OR sapajus OR cyprinodontiformes OR hippopotamus OR pelophylax OR capybara OR capybaras OR weasel OR weasels OR cairina OR cynomys OR lutra OR cockatoo OR cockatoos OR lachesis OR lagomorpha OR rupicapra OR daboia OR "orang utan" OR "orang utans" OR platyrrhini OR charadriiformes OR micrurus OR psittaciformes OR spalax OR loris OR mustelidae OR sylvilagus OR vitticeps OR cockatiel OR mustelus OR cottus OR erythrocebus OR dipodomys OR platessa OR callicebus OR loricariidae OR catostomus OR cuneata OR cyanistes OR cyprinodon OR sigmodontinae OR elasmobranchii OR trichechus OR sauropsid OR xenarthra OR dormouse OR perissodactyla OR nautilus OR cirrhinus OR gulo OR gulos OR tragelaphus OR merula OR numida OR sciaenidae OR cerastes OR sciuridae OR gibbosus OR octopuses OR eland OR elands OR phyllomedusa OR pogona OR walrus OR agamidae OR leptodactylidae OR ridibundus OR leontopithecus OR anteater OR anteaters OR pelodiscus OR cebidae OR columbianus OR "pelteobagrus fulvidraco" OR hominoidea OR mandrillus OR "zonotrichia leucophrys" OR agama OR gobiocypris OR "bearded dragon" OR "bearded dragons" OR sarotherodon OR talpa OR discoglossus OR hagfishes OR sphenodon OR gudgeon OR amphiuma OR aythya OR tenrec OR tenrec OR hominidae OR risoria OR salamandridae OR camelidae OR columbiformes OR latimeria OR plover OR plovers OR afrotheria OR "falco sparverius" OR polecat OR polecats OR crotalinae OR salvadora OR tarsier OR lucioperca OR anchovies OR lungfishes OR terrapin OR "dromaius novaehollandiae" OR lateolabrax OR eigenmannia OR pelamis OR theropithecus OR murinae OR gander OR gymnotus OR pseudacris OR gymnophiona OR gymnotiformes OR laticauda OR falconiformes OR dugong OR dugongs OR pintail OR pintails OR rook OR rooks OR lasiurus OR catshark OR catsharks OR micropogonias OR "red junglefowl" OR paddlefish OR eutheria OR ophiophagus OR hollandicus OR nymphicus OR pimelodidae OR aepyceros OR cobitidae OR strigiformes OR cobitis OR dormice OR alytes OR calloselasma OR guanaco OR guanacos OR phasianidae OR "round goby" OR trichogaster OR catarrhini OR eelpout OR eelpouts OR galaxias OR gaur OR pungitius OR suslik OR susliks OR flatfishes OR percidae OR caprinae OR todarodes OR osmerus OR ameiurus OR anthropoidea OR "castor canadensis" OR pouting OR poutings OR tetraodontiformes OR arvicolinae OR siamang OR siamangs OR "castor fiber" OR nomascus OR "red knot" OR "red knots" OR syngnathidae OR iguanidae OR eretmochelys OR ursidae OR callimico OR columbidae OR microhylidae OR anaxyrus OR menidia OR pipistrelle OR greylag OR pipidae OR scandentia OR bowfin OR bowfins OR dendrobatidae OR zenaida OR bushbaby OR harrier OR harriers OR macropodidae OR pygerythrus OR clupeidae OR odorrana OR corvidae OR jerboa OR jerboas OR canutus OR hylobatidae OR clupeiformes OR "great cormorant" OR "great cormorants" OR scorpaeniformes OR chondrostean OR garfish OR proboscidea OR psetta OR diapsid OR serotinus OR tetrao OR walruses OR carcharhiniformes OR leucoraja OR pumpkinseed OR dosidicus OR acipenseriformes OR daubentonii OR emberizidae OR gadiformes OR hyraxes OR stizostedion OR wolverine OR wolverines OR lissotriton OR acanthurus OR centrarchidae OR gloydius OR laurasiatheria OR limosa OR psittacula OR leporidae OR proteidae OR zander OR zanders OR arapaima OR bagridae OR cyprinodontidae OR mithun OR pandion OR jackdaw OR jackdaws OR procyonidae OR carus OR jaculus OR salmoniformes OR "common sole" OR "common soles"

	OR protobothrops OR calamita OR brachyteles OR trionyx OR turdidae OR boidae OR luscinia OR pugnax OR euarchontoglires OR saithe OR saithes OR symphalangus OR aardvark OR aardvarks OR oystercatcher OR oystercatchers OR arius OR corydoras OR poacher OR poachers OR aurochs OR cebuella OR crecca OR lemuridae OR sirenia OR lemmus OR perdix OR glires OR lepidosaur OR muskox OR deinagkistrodon OR pholidota OR holocephali OR cercopithecinae OR clariidae OR agapornis OR doryteuthis OR tyrannidae OR dicroglossidae OR godwit OR godwits OR monedula OR pongidae OR atheriniformes OR colobinae OR lophocebus OR atelidae OR cottidae OR leucopsis OR acanthuridae OR didelphimorphia OR elver OR elvers OR lapponica OR dermoptera OR "european hake" OR "european hakes" OR gerbillinae OR banteng OR hartebeest OR hartebeests OR hogget OR haematopus OR "anguis fragilis" OR "grey heron" OR "grey herons" OR "blue whiting" OR "blue whitings" OR furnariidae OR macrovipera OR esocidae OR lapwing OR lapwings OR mylopharyngodon OR wallabia OR beloniformes OR potoroo OR potoroos OR "athene noctua" OR pleuronectidae OR bushbabies OR muscicapidae OR alligatoridae OR fuligula OR "bush baby" OR guineafowl OR spoonbill OR spoonbills OR viverridae OR catostomidae OR zebrafishes OR ibexes OR vendace OR estrildidae OR monotremata OR sepiella OR ambystomatidae OR shelduck OR shelducks OR treeshrew OR treeshrews OR hoplobatrachus OR pochard OR hoolock OR hoolocks OR lynxes OR antilope OR antilopes OR blackbuck OR blackbucks OR cricetinae OR paramisgurnus OR skylark OR skylarks OR soleidae OR allobates OR "northern wheatear" OR "northern wheatears" OR pitheciidae OR takin OR theria OR vanellus OR galaxiidae OR lorisidae OR ostralegus OR palaeognathae OR "stone loach" OR alauda OR callitrichinae OR caniformia OR duttaphrynus OR ictaluridae OR osteoglossiformes OR poultries OR curema OR "ruddy turnstone" OR "ruddy turnstones" OR sheatfish OR sunfishes OR centropomidae OR hemachatus OR platalea OR thamnophilidae OR "song thrush" OR atherinopsidae OR siluridae OR tadorna OR chroicocephalus OR ermine OR ermines OR gavialis OR ruffe OR tupaiidae OR diprotodontia OR hyaenidae OR antilopinae OR crocodylidae OR herpestidae OR hippopotamidae OR "northern shoveler" OR "round gobies" OR cheirogaleidae OR indriidae OR fundulidae OR pythonidae OR rhynchocephalia OR anodorhynchus OR "red-backed shrike" OR "red-backed shrikes" OR triakidae OR phalangeridae OR aoudad OR boreoeutheria OR "eurasian jay" OR "eurasian jays" OR feliformia OR haplorhini OR osteoglossidae OR paenungulata OR struthioniformes OR ferina OR sanderling OR sanderlings OR spheniscidae OR cuttlefishes OR cygnet OR dasycneme OR gadwall OR gadwalls OR "pelobates fuscus" OR wryneck OR wrynecks OR afrosoricida OR culaea OR "dover sole" OR "dover soles" OR paralichthyidae OR passeridae OR osteolaemus OR "song thrushes" OR bluethroat OR bluethroats OR hydrophiidae OR megrim OR mephitidae OR strepsirhini OR tomistoma OR epidalea OR osmeriformes OR "bush babies" OR tarsiiform OR atelinae OR bufotes OR "eurasian coot" OR "eurasian coots" OR galagidae OR geopelia OR philomachus OR tubulidentata OR bombinatoridae OR pelobatidae OR tachysurus OR ailuridae OR woodlark OR woodlarks OR alcelaphinae OR redshank OR redshanks OR salientia OR "sand smelt" OR "sand smelts" OR woodmice OR woodmouse OR dasyproctidae OR "eurasian wigeon" OR "eurasian wigeons" OR garganey OR garganeys OR "lemon sole" OR "lemon soles" OR "common dab" OR "common dabs" OR graylag OR graylags OR leucorodia OR osphronemidae OR bewickii OR "common moorhen" OR "common moorhens" OR decapodiformes OR gobbler OR gobblers OR odontophoridae OR

	paddlefishes OR salmonine OR esociformes OR "eurasian woodcock" OR "eurasian woodcocks" OR "european smelt" OR "european smelts" OR goldfishes OR tenches OR tyranni OR "common chaffinch" OR "common chaffinchs" OR "common redstart" OR "common redstarts" OR "common roach" OR "common roachs" OR "great knot" OR "great knots" OR potoroidae OR alytidae OR coregonine OR dipteral OR leveret OR "poeciliopsis gracilis" OR amphiumidae OR batrachoidiformes OR "bighead goby" OR heteropneustidae OR lullula OR "norway pout" OR "norway pouts" OR sipunculida OR dogfishes OR sebastidae OR tarsiidae OR alethinophidia OR "common nase" OR "common nases" OR "common sandpiper" OR "common sandpipers" OR "eurasian blackcap" OR "eurasian blackcaps" OR pterocnemia OR syngnathiformes OR "common chaffinches" OR eupleridae OR octopodiformes OR phascolarctidae OR scophthalmidae OR "starry smooth-hound" OR "starry smooth-hounds" OR whitefishes OR cuniculidae OR "european sprat" OR "european sprats" OR "rosy bitterling" OR "rosy bitterlings" OR "common dace" OR "common daces" OR "lesser weever" OR "lesser weevers" OR scaldfish OR "water rail" OR "water rails" OR alouattinae OR centrarchiformes OR "common whitethroat" OR "common whitethroats" OR gavialidae OR "grey gurnard" OR "grey gurnards" OR lateolabracidae OR rheiformes OR "tub gurnard" OR "tub gurnards" OR "common chiffchaff" OR "common chiffchaffs" OR garfishes OR "lesser whitethroat" OR "lesser whitethroats" OR myoxidae OR seabasses OR spariformes OR umbridae OR "yellow boxfish" OR anabantiformes OR aotidae OR "common bleak" OR "common bleaks" OR "common rudd" OR "common rudds" OR "greater pipefish" OR hapale OR nandiniidae OR "stone loaches" OR whinchat OR whinchats OR acanthuriformes OR "brotula barbata" OR "common ling" OR "common lings" OR "common roaches" OR cottonrat OR cottonrats OR douroucoulis OR dromaiidae OR fitches OR fitchew OR galaxiiformes OR laprine OR saimiriinae OR solenette OR tarsii OR "tompot blenny" OR "common dragonet" OR "common dragonets" OR "longspined bullhead" OR "longspined bullheads" OR monotremate OR monotremates OR pempheriformes OR perdicinae OR presbytini OR smegmamorpha OR "bighead gobies" OR "carangaria incertae sedis" OR coiidae OR "fivebeard rockling" OR foulmart OR foumart OR grasskeet OR "greater pipefishes" OR ibices OR millionfish OR muguliformes OR "norwegian topknot" OR peewit OR "red sea sailfin tang" OR rupicapras OR sheatfishes OR "tompot blennies" OR "twait shad" OR "yellow boxfishes") 2: TS=(myelomeningocele or meningomyelocele or meningocele) 3: TS=(spinal dysraphism* or spina bifida) 4: TS=(arnold-chiari or chiari) 5: TS=stem 6: TS=patch* 7: #2 OR #3 OR #4 8: #5 OR #6 9: #8 AND #7 AND #1
SCOPUS	TITLE-ABS-KEY (rat OR rats OR animal OR animals OR mice OR "in vivo" OR mouse OR rabbit OR rabbits OR murine OR pig OR pigs OR dog OR dogs OR bovine OR fish OR vertebrate OR vertebrates OR cat OR cats OR rodent OR rodents OR mammal OR mammals OR chicken OR chickens OR monkey OR monkeys OR sheep OR canine OR canines OR porcine OR cattle OR bird OR birds OR hamster OR hamsters OR primate OR primates OR cow OR cows OR chick OR horse OR horses OR avian OR avians OR calf OR swine OR swines OR xenopus OR turkeys

	OR bear OR bears OR frog OR frogs OR zebrafish OR goat OR goats OR equine OR calves OR poultry OR macaque OR macaques OR mole OR moles OR ovine OR lamb OR lambs OR fishes OR diptera OR amphibian OR amphibians OR snake OR snakes OR ruminant OR ruminants OR hen OR hens OR piglet OR piglets OR feline OR felines OR simian OR simians OR laevis OR trout OR trouts OR teleost OR teleosts OR salmon OR salmons OR seal OR seals OR bull OR bulls OR ewe OR ewes OR hedgehog OR hedgehogs OR macaca OR macacas OR proteus OR pigeon OR pigeons OR bat OR bats OR duck OR ducks OR chimpanzee OR chimpanzees OR baboon OR baboons OR deer OR rana OR ranas OR carp OR carps OR heifer OR swallow OR swallows OR lizard OR lizards OR canis OR sow OR sows OR cynomolgus OR quail OR quails OR reptile OR reptiles OR turtle OR turtles OR buffalo OR gerbil OR gerbils OR boar OR boars OR squirrel OR squirrels OR oncorhynchus OR mus OR toad OR toads OR fowl OR fowls OR rerio OR danio OR ara OR aras OR musculus OR tadpole OR tadpoles OR mulatta OR salmo OR ram OR eagle OR eagles OR ferret OR ferrets OR goldfish OR catfish OR whale OR whales OR fox OR foxes OR ape OR apes OR elephant OR elephants OR bos OR marmoset OR marmosets OR cod OR cods OR shark OR sharks OR wolf OR eel OR eels OR auratus OR rattus OR zebra OR zebras OR tilapia OR tilapias OR gilt OR camel OR camels OR squid OR gallus OR marsupial OR marsupials OR vole OR voles OR fascicularis OR ovis OR salmonid OR salmonids OR tiger OR tigers OR dolphin OR dolphins OR robin OR robins OR carpio OR opossum OR opossums OR cyprinus OR salamander OR salamanders OR felis OR mink OR minks OR swan OR swans OR norvegicus OR bufo OR torpedo OR bass OR lamprey OR lampreys OR sus OR python OR pythons OR tetrapod OR tetrapods OR shrew OR shrews OR lion OR lions OR hog OR hogs OR songbird OR songbirds OR oreochromis OR starling OR starlings OR caprine OR carassius OR owl OR owls OR newt OR newts OR papio OR scrofa OR hare OR hares OR gorilla OR gorillas OR flounder OR flounders OR goose OR herring OR herrings OR therian OR buffaloes OR canary OR sparrow OR sparrows OR microtus OR octopus OR troglodytes OR tuna OR amphibia OR chinchilla OR chinchillas OR ide OR oryzias OR cervus OR kangaroo OR kangaroos OR armadillo OR armadillos OR callithrix OR "pan troglodytes" OR saimiri OR cichlid OR cichlids OR donkey OR donkeys OR bream OR char OR chars OR finch OR raccoon OR raccoons OR bothrops OR anguilla OR perch OR cricetus OR seabird OR seabirds OR buck OR bucks OR naja OR coturnix OR salmonids OR geese OR minnow OR minnows OR raptor OR raptors OR merione OR meriones OR rodentia OR elaphus OR amniote OR amniotes OR elasmobranch OR emu OR emus OR peromyscus OR hominid OR hominids OR bubalus OR crotalus OR gull OR gulls OR anas OR anura OR lemur OR lemurs OR crow OR crows OR camelus OR gibbon OR gibbons OR waterfowl OR parrot OR parrots OR eels OR cob OR stickleback OR sticklebacks OR columba OR mesocricetus OR ambystoma OR raven OR ravens OR gadus OR penguin OR penguins OR orangutan OR orangutans OR sturgeon OR sturgeons OR cuniculus OR aves OR virginianus OR cephalopod OR cephalopods OR cebus OR sparus OR tortoise OR tortoises OR guttata OR morhua OR unguiculatus OR dogfish OR vulpes OR mallard OR mallards OR apodemus OR alligator OR alligators OR oryctolagus OR llama OR llamas OR reindeer OR mustela OR duckling OR ducklings OR wolves OR sander OR amazona OR zebu OR badger OR badgers OR dove OR doves OR ictalurus OR capra OR capras OR equus OR camelid OR camelids OR poecilia OR mule OR mules OR perciformes OR salvelinus OR labrax OR cyprinidae OR ariidae OR crocodile OR crocodiles OR fundulus OR dicentrarchus OR clarias OR cercopithecus OR chiroptera OR alpaca OR alpacas OR pike OR pikes OR paralichthys OR puma OR pumas OR

	didelphis OR pisces OR macropus OR triturus OR bison OR bisons OR epinephelus OR gasterosteus OR panthera OR acipenser OR mackerel OR mackerels OR tamarin OR tamarins OR ostrich OR anolis OR vervet OR vervets OR wallaby OR glareolus OR beaver OR beavers OR dromedary OR catus OR killifish OR pimephales OR promelas OR aotus OR phoca OR panda OR pandas OR porpoise OR porpoises OR myotis OR yak OR yaks OR agkistrodon OR vipera OR otter OR otters OR turbot OR turbots OR squamate OR carnivora OR mullet OR mullets OR hawk OR hawks OR taeniopygia OR seahorse OR seahorses OR "poecilia reticulata" OR falcon OR falcons OR prosimian OR prosimians OR parus OR perca OR fingerling OR fingerlings OR antelope OR antelopes OR tupaia OR passeriformes OR sepia OR saguinus OR coyote OR coyotes OR pongo OR meleagris OR reptilia OR lepus OR psittacine OR hagfish OR warbler OR warblers OR "russell s viper" OR "russell s vipers" OR smolt OR smolts OR budgerigar OR sardine OR sardines OR cavia OR cavias OR hyla OR pleurodeles OR siluriformes OR "great tit" OR "great tits" OR guppy OR bonobo OR bonobos OR rutilus OR trichosurus OR muridae OR phodopus OR channa OR squalus OR lynx OR sturnus OR petromyzon OR vitulina OR monodelphis OR cuttlefish OR adder OR adders OR lepomis OR canaria OR gambusia OR guppies OR xiphophorus OR flatfish OR koala OR koalas OR labeo OR stingray OR stingrays OR chelonia OR lampetra OR spermophilus OR crocodilian OR "passer domesticus" OR sciurus OR artiodactyla OR ranidae OR corvus OR necturus OR platypus OR canaries OR bovid OR lagopus OR trimeresurus OR gariepinus OR marten OR martens OR drosophilidae OR mugil OR sunfish OR porcellus OR cypriniformes OR alouatta OR scophthalmus OR anser OR electrophorus OR putorius OR iguana OR iguanas OR lama OR lamas OR takifugu OR circus OR eptesicus OR flycatcher OR galago OR galagos OR trachemys OR lungfish OR characiformes OR shorebird OR shorebirds OR giraffe OR giraffes OR micropterus OR scyliorhinus OR cichlidae OR loligo OR porcupine OR porcupines OR chub OR chubs OR solea OR pleuronectes OR hylidae OR viperidae OR echis OR sorex OR anchovy OR lagomorph OR ostriches OR vulture OR vultures OR whitefish OR araneus OR jird OR jirds OR tern OR esox OR drake OR drakes OR elapidae OR gallopavo OR chordata OR myodes OR caretta OR serinus OR grouse OR misgurnus OR meles OR blackbird OR blackbirds OR coregonus OR bobwhite OR bobwhites OR heteropneustes OR mammoth OR mammoths OR turdus OR rhinella OR ateles OR characidae OR clupea OR bungarus OR brill OR "struthio camelus" OR sloth OR sloths OR pteropus OR sculpin OR anthropoids OR pollock OR pollocks OR morone OR "pan paniscus" OR litoria OR chipmunk OR chipmunks OR balaenoptera OR marmota OR melopsittacus OR hyrax OR lemming OR lemmings OR halibut OR hylobates OR lates OR caiman OR caimans OR sigmodon OR stenella OR barbel OR barbels OR sterna OR parakeet OR parakeets OR phocoena OR leptodactylus OR canidae OR buteo OR harengus OR gopher OR gophers OR marmot OR marmots OR gosling OR goslings OR platichthys OR gar OR gars OR sebastes OR marsupialia OR notophthalmus OR gazelle OR gazelles OR insectivora OR paridae OR felidae OR russula OR galliformes OR bombina OR colobus OR echidna OR echidnas OR seabass OR syncerus OR plaice OR "blue tit" OR "blue tits" OR pagrus OR catfishes OR cetacea OR barbus OR cygnus OR ficedula OR chamois OR colubridae OR perches OR coelacanth OR fitch OR urodela OR cynops OR martes OR halichoerus OR aix OR salmonidae OR leuciscus OR magpie OR magpies OR silurus OR whiting OR whitings OR anseriformes OR colinus OR rhea OR chlorocebus OR octodon OR acinonyx OR mouflon OR mouflons OR ibex OR tetraodon OR bufonidae OR equidae OR jackal OR cephalopoda OR dendroaspis OR glama OR muskrat OR muskrats OR

	sable OR sables OR wildebeest OR streptopelia OR albifrons OR vespertilionidae OR woodpecker OR woodpeckers OR muntjac OR muntjacs OR archosaur OR branta OR cricetulus OR megalobrama OR poeciliidae OR desmodus OR snakehead OR snakeheads OR tench OR teal OR teals OR bandicoot OR bandicoots OR apteronotus OR phyllostomidae OR crocidura OR buzzard OR buzzards OR larimichthys OR cercocebus OR pipistrellus OR erithacus OR impala OR impalas OR rousettus OR haddock OR haddocks OR tinca OR ratite OR calidris OR cynoglossus OR hypophthalmichthys OR bullock OR bullocks OR dromedaries OR alectoris OR filly OR salamandra OR cingulata OR bitis OR grus OR ammodytes OR macaw OR macaws OR hypoleuca OR sapajus OR cyprinodontiformes OR hippopotamus OR pelophylax OR capybara OR capybaras OR weasel OR weasels OR cairina OR cynomys OR lutra OR cockatoo OR cockatoos OR lachesis OR lagomorpha OR rupicapra OR daboia OR "orang utan" OR "orang utans" OR platyrrhini OR charadriiformes OR micrurus OR psittaciformes OR spalax OR loris OR mustelidae OR sylvilagus OR vitticeps OR cockatiel OR mustelus OR cottus OR erythrocebus OR dipodomys OR platessa OR callicebus OR loricariidae OR catostomus OR cuneata OR cyanistes OR cyprinodon OR sigmodontinae OR elasmobranchii OR trichechus OR sauropsid OR xenarthra OR dormouse OR perissodactyla OR nautilus OR cirrhinus OR gulo OR gulos OR tragelaphus OR merula OR numida OR sciaenidae OR cerastes OR sciuridae OR gibbosus OR octopuses OR eland OR elands OR phyllomedusa OR pogona OR walrus OR agamidae OR leptodactylidae OR ridibundus OR leontopithecus OR anteater OR anteaters OR pelodiscus OR cebidae OR columbianus OR "pelteobagrus fulvidraco" OR hominoidea OR mandrillus OR "zonotrichia leucophrys" OR agama OR gobiocypris OR "bearded dragon" OR "bearded dragons" OR sarotherodon OR talpa OR discoglossus OR hagfishes OR sphenodon OR gudgeon OR amphiuma OR aythya OR tenrec OR tenrec OR hominidae OR risoria OR salamandridae OR camelidae OR columbiformes OR latimeria OR plover OR plovers OR afrotheria OR "falco sparverius" OR polecat OR polecats OR crotalinae OR salvadora OR tarsier OR lucioperca OR anchovies OR lungfishes OR terrapin OR "dromaius novaehollandiae" OR lateolabrax OR eigenmannia OR pelamis OR theropithecus OR murinae OR gander OR gymnotus OR pseudacris OR gymnophiona OR gymnotiformes OR laticauda OR falconiformes OR dugong OR dugongs OR pintail OR pintails OR rook OR rooks OR lasiurus OR catshark OR catsharks OR micropogonias OR "red junglefowl" OR paddlefish OR eutheria OR ophiophagus OR hollandicus OR nymphicus OR pimelodidae OR aepyceros OR cobitidae OR strigiformes OR cobitis OR dormice OR alytes OR calloselasma OR guanaco OR guanacos OR phasianidae OR "round goby" OR trichogaster OR catarrhini OR eelpout OR eelpouts OR galaxias OR gaur OR pungitius OR suslik OR susliks OR flatfishes OR percidae OR caprinae OR todarodes OR osmerus OR ameiurus OR anthropoidea OR "castor canadensis" OR pouting OR poutings OR tetraodontiformes OR arvicolinae OR siamang OR siamangs OR "castor fiber" OR nomascus OR "red knot" OR "red knots" OR syngnathidae OR iguanidae OR eretmochelys OR ursidae OR callimico OR columbidae OR microhylidae OR anaxyrus OR menidia OR pipistrelle OR greylag OR pipidae OR scandentia OR bowfin OR bowfins OR dendrobatidae OR zenaida OR bushbaby OR harrier OR harriers OR macropodidae OR pygerythrus OR clupeidae OR odorrana OR corvidae OR jerboa OR jerboas OR canutus OR hylobatidae OR clupeiformes OR "great cormorant" OR "great cormorants" OR scorpaeniformes OR chondrostean OR garfish OR proboscidea OR psetta OR diapsid OR serotinus OR tetrao OR walruses OR carcharhiniformes OR leucoraja OR pumpkinseed OR dosidicus OR acipenseriformes OR

	daubentonii OR emberizidae OR gadiformes OR hyraxes OR stizostedion OR wolverine OR wolverines OR lissotriton OR acanthurus OR centrarchidae OR gloydius OR laurasiatheria OR limosa OR psittacula OR leporidae OR proteidae OR zander OR zanders OR arapaima OR bagridae OR cyprinodontidae OR mithun OR pandion OR jackdaw OR jackdaws OR procyonidae OR carus OR jaculus OR salmoniformes OR "common sole" OR "common soles" OR protobothrops OR calamita OR brachyteles OR trionyx OR turdidae OR boidae OR luscinia OR pugnax OR euarchontoglires OR saithe OR saithes OR symphalangus OR aardvark OR aardvarks OR oystercatcher OR oystercatchers OR arius OR corydoras OR poacher OR poachers OR aurochs OR cebuella OR crecca OR lemuridae OR sirenia OR lemmus OR perdix OR glires OR lepidosaur OR muskox OR deinagkistrodon OR pholidota OR holocephali OR cercopithecinae OR clariidae OR agapornis OR doryteuthis OR tyrannidae OR dicroglossidae OR godwit OR godwits OR monedula OR pongidae OR atheriniformes OR colobinae OR lophocebus OR atelidae OR cottidae OR leucopsis OR acanthuridae OR didelphimorphia OR elver OR elvers OR lapponica OR dermoptera OR "european hake" OR "european hakes" OR gerbillinae OR banteng OR hartebeest OR hartebeests OR hogget OR haematopus OR "anguis fragilis" OR "grey heron" OR "grey herons" OR "blue whiting" OR "blue whitings" OR furnariidae OR macrovipera OR esocidae OR lapwing OR lapwings OR mylopharyngodon OR wallabia OR beloniformes OR potoroo OR potoroos OR "athene noctua" OR pleuronectidae OR bushbabies OR muscicapidae OR alligatoridae OR fuligula OR "bush baby" OR guineafowl OR spoonbill OR spoonbills OR viverridae OR catostomidae OR zebrafishes OR ibexes OR vendace OR estrildidae OR monotremata OR sepiella OR ambystomatidae OR shelduck OR shelducks OR treeshrew OR treeshrews OR hoplobatrachus OR pochard OR hoolock OR hoolocks OR lynxes OR antilope OR antilopes OR blackbuck OR blackbucks OR cricetinae OR paramisgurnus OR skylark OR skylarks OR soleidae OR allobates OR "northern wheatear" OR "northern wheatears" OR pitheciidae OR takin OR theria OR vanellus OR galaxiidae OR lorisidae OR ostralegus OR palaeognathae OR "stone loach" OR alauda OR callitrichinae OR caniformia OR duttaphrynus OR ictaluridae OR osteoglossiformes OR poultries OR curema OR "ruddy turnstone" OR "ruddy turnstones" OR sheatfish OR sunfishes OR centropomidae OR hemachatus OR platalea OR thamnophilidae OR "song thrush" OR atherinopsidae OR siluridae OR tadorna OR chroicocephalus OR ermine OR ermines OR gavialis OR ruffe OR tupaiidae OR diprotodontia OR hyaenidae OR antilopinae OR crocodylidae OR herpestidae OR hippopotamidae OR "northern shoveler" OR "round gobies" OR cheirogaleidae OR indriidae OR fundulidae OR pythonidae OR rhynchocephalia OR anodorhynchus OR "red-backed shrike" OR "red-backed shrikes" OR triakidae OR phalangeridae OR aoudad OR boreoeutheria OR "eurasian jay" OR "eurasian jays" OR feliformia OR haplorhini OR osteoglossidae OR paenungulata OR struthioniformes OR ferina OR sanderling OR sanderlings OR spheniscidae OR cuttlefishes OR cygnet OR dasycneme OR gadwall OR gadwalls OR "pelobates fuscus" OR wryneck OR wrynecks OR afrosoricida OR culaea OR "dover sole" OR "dover soles" OR paralichthyidae OR passeridae OR osteolaemus OR "song thrushes" OR bluethroat OR bluethroats OR hydrophiidae OR megrim OR mephitidae OR strepsirhini OR tomistoma OR epidalea OR osmeriformes OR "bush babies" OR tarsiiform OR atelinae OR bufotes OR "eurasian coot" OR "eurasian coots" OR galagidae OR geopelia OR philomachus OR tubulidentata OR bombinatoridae OR pelobatidae OR tachysurus OR ailuridae OR woodlark OR woodlarks OR alcelaphinae OR redshank OR redshanks OR salientia OR "sand smelt" OR "sand smelts" OR

	woodmice OR woodmouse OR dasyproctidae OR "eurasian wigeon" OR "eurasian wigeons" OR garganey OR garganeys OR "lemon sole" OR "lemon soles" OR "common dab" OR "common dabs" OR graylag OR graylags OR leucorodia OR osphronemidae OR bewickii OR "common moorhen" OR "common moorhens" OR decapodiformes OR gobbler OR gobblers OR odontophoridae OR paddlefishes OR salmonine OR esociformes OR "eurasian woodcock" OR "eurasian woodcocks" OR "european smelt" OR "european smelts" OR goldfishes OR tenches OR tyranni OR "common chaffinch" OR "common chaffinchs" OR "common redstart" OR "common redstarts" OR "common roach" OR "common roachs" OR "great knot" OR "great knots" OR potoroidae OR alytidae OR coregonine OR dipteral OR leveret OR "poeciliopsis gracilis" OR amphiumidae OR batrachoidiformes OR "bighead goby" OR heteropneustidae OR lullula OR "norway pout" OR "norway pouts" OR sipunculida OR dogfishes OR sebastidae OR tarsiidae OR alethinophidia OR "common nase" OR "common nases" OR "common sandpiper" OR "common sandpipers" OR "eurasian blackcap" OR "eurasian blackcaps" OR pterocnemia OR syngnathiformes OR "common chaffinches" OR eupleridae OR octopodiformes OR phascolarctidae OR scophthalmidae OR "starry smooth-hound" OR "starry smooth-hounds" OR whitefishes OR cuniculidae OR "european sprat" OR "european sprats" OR "rosy bitterling" OR "rosy bitterlings" OR "common dace" OR "common daces" OR "lesser weever" OR "lesser weevers" OR scaldfish OR "water rail" OR "water rails" OR alouattinae OR centrarchiformes OR "common whitethroat" OR "common whitethroats" OR gavialidae OR "grey gurnard" OR "grey gurnards" OR lateolabracidae OR rheiformes OR "tub gurnard" OR "tub gurnards" OR "common chiffchaff" OR "common chiffchaffs" OR garfishes OR "lesser whitethroat" OR "lesser whitethroats" OR myoxidae OR seabasses OR spariformes OR umbridae OR "yellow boxfish" OR anabantiformes OR aotidae OR "common bleak" OR "common bleaks" OR "common rudd" OR "common rudds" OR "greater pipefish" OR hapale OR nandiniidae OR "stone loaches" OR whinchat OR whinchats OR acanthuriformes OR "brotula barbata" OR "common ling" OR "common lings" OR "common roaches" OR cottonrat OR cottonrats OR douroucoulis OR dromaiidae OR fitches OR fitchew OR galaxiiformes OR laprine OR saimiriinae OR solenette OR tarsii OR "tompot blenny" OR "common dragonet" OR "common dragonets" OR "longspined bullhead" OR "longspined bullheads" OR monotremate OR monotremates OR pempheriformes OR perdicinae OR presbytini OR smegmamorpha OR "bighead gobies" OR "carangaria incertae sedis" OR coiidae OR "fivebeard rockling" OR foulmart OR foumart OR grasskeet OR "greater pipefishes" OR ibices OR millionfish OR muguliformes OR "norwegian topknot" OR peewit OR "red sea sailfin tang" OR rupicapras OR sheatfishes OR "tompot blennies" OR "twait shad" OR "yellow boxfishes") AND TITLE-ABS-KEY (myelomeningocele OR meningomyelocele OR meningocele OR spinal AND dysraphism* OR spina AND bifida OR arnold-chiari OR chiari) AND TITLE-ABS-KEY (stem OR patch*)

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