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Anatomical features for an adequate choice of the experimental animal model in biomedicine: *II.* Small laboratory rodents, rabbit, and pig

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SUMMARY

The anatomical features distinctive of each of the very large array of species used in today's biomedical research are important to be considered in a correct choice of the animal model(s), particularly when translational research is concerned. In this paper we take into consideration and discuss the most important anatomical and histological features of the commonest species of laboratory rodents (rat, mouse, guinea pig, hamster, and gerbil), rabbit, and pig related to their importance for applied research.

1. Animals as models in today's biomedicine

Scientific research is intimately linked to the nature of human beings: it is the pursuit for new knowledge and the discovery of the unknown. In today's culture, scientific research is

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somehow regarded as a synonymous of progress. This idea is strongly linked to the social perception of science in terms of its importance for mankind development. What is currently defined as *basic research* is a fundamentally theoretical or experimental investigation that aims to advance knowledge, without specifically envisaged and/or immediate practical applications. A risk that is related to this definition is that basic research is perceived as an economically unnecessary luxury. As a logical consequence of this type of reasoning, a line of though is that it should be better replaced by *applied research*, which has a practical impact in a reasonably short frame of time and more directly addresses immediate societal needs (Gibbons et al., 1994). Under this perspective, the term *translational research* has rapidly caught over to somehow fill this potentially very dangerous dichotomy between basic and applied research. A PubMed search for the string «translational research» (between quotation marks) yielded 11,088 items in June 2015. Occurrences for 2014 were 2,743, and the term first appeared in 1993 with only one occurrence. It is noteworthy that, in parallel with the introduction of the term translational research in the biomedical literature, Gibbons et al. (1994) have defined a new *Mode 2 of knowledge production* that, according to these authors, was emerging alongside the more traditional and familiar *Mode 1* that is what was usually defined as *science*. They coined the expression *Mode 1 of knowledge production* to summarize with it the ensemble of the cognitive and social norms that must be followed in the production, validation and diffusion of sound scientific information. With Mode 2 knowledge they, instead, intended a type of knowledge that was, generally speaking, of immediate use for the society and its stakeholders in industry and government. Thus, basic research immediately falls into the Mode 1 knowledge definition, and applied/translational research into that of Mode 2. This type of framework has assumed increasing importance, and is now also at the basis of the funding policies in most Universities and public bodies (Hessels and van Lente, 2008). It immediately follows that research perspectives in the field of Anatomy

and related disciplines have been dramatically changed in the two past decades with lesser emphasis for purely comparative studies (Mode 1) and an increasing attention for observations that have some translational potential (Mode 2).

In this context and in parallel with the due consideration for the ethics of animal experimentation, animals in scientific research are no longer considered merely as passive tools, but rather as complex models that are indispensable to move from observations to theory. The discussion of the theory that lies behind the principles of biomedical modeling (Massoud et al., 1998) is beyond our purposes. Yet it is important, at this point, trying to consider what is an *ideal animal model,* since, from one side, complexity itself makes live animals appealing models, but, pushing our reasoning to the extreme limit, the only correct model for translational studies should be another human being. Although complexity may be desirable, simpler and less confounding biological models are clearly needed (D'Angelo et al., 2015). In biomedical research, *model* is used synonymously with *analog* to mean a living being that is similar in function to what is to be modeled (the human organism in translational research), but that may differ in structure (being simpler) and origin from it. Thus, the model (analog) both simplifies and puts into a more easily understandable context a complicated subject, thereby enabling one to think much more clearly about the subject itself (Massoud et al., 1998).

On these premises it is clear that the first and most important parameter to be considered in the choice of a valid animal model is whether or not it accurately mimics the desired function or disease, and if data can be indeed extrapolated to man. However, several other parameters have to be taken into consideration, which are primarily related to species-specific features such as *e.g.* availability, life-span and survival, size, multiparity, easiness and cheapness in handling and housing.

Here, we will consider the mammals most widely employed in biomedical research (rat, mouse, rabbit, guinea-pig, golden hamster, and pig) and describe the most important *species-specific anatomical features* that may be relevant for a proper identification of a given species as a model in translational studies. With the same objectives, the anatomical characteristics of the most diffused fish models are considered in a companion paper (D'Angelo et al., 2015).

It should be noted that addressing the issues of strain-related differences and reliability of transgenic models is beyond the purpose of our contributions - see *e.g.* Rohra et al. (2005) for an interesting discussion of these matters. Obviously, we likewise will not resume here the amount of literature on the rat and mouse nervous system where anatomical and histological differences with humans may be very specific, as *e.g.* is the case of the localization of the cortico-spinal tract in the dorsal funiculus of the rat (rodent) spinal cord (Courtine et al., 2007), or very subtle, as *e.g.* it is the case for interspecies differences in the organization of the somatosensory circuitries (Merighi et al., 2008; Ferrini et al., 2014). Also, we will not consider here some specificities related to spontaneous rat/mouse mutants (D'Arcangelo, 2006; Castagna et al., 2014; Loscher, 2010) or experimentally generated transgenics (Bilkei-Gorzo, 2014; Do and Cuello, 2013; Hochgrafe and Mandelkow, 2013).

Our primary aim is instead to put under the spotlights the importance of a sound anatomical knowledge as an indispensable prerequisite for proper experimental planning of basic research studies aiming to move towards a translation to humans. As a general introduction, Table 1 reports a summary of the main current uses of individual species in research, whereas some general anatomical features are summarized in Table 2.

In describing each species, we provide: *i.* general information on its origin, biology and use in biomedical research; *ii.* an overall description of the main anatomical features; *iii.* a description of the specific embryological, histological and anatomical characteristics that

differ from those in humans, and that we believe are relevant in translational studies. The latter part is patently the core of the review.

Finally, it should be mentioned that we have totally neglected interspecies behavioral differences, or only briefly mentioned those that are of interest for modelling some specific physiological or pathological conditions, as there is an extremely wide literature on these aspect in terms of ethology and general biology.

2. Mouse

2.1 Origin, general biology, and use in biomedical research

Mice are grouped with rats in the order *Rodentia*, suborder *Myomorpha*, family *Muridae*. Mice evolved relatively recently in South Asia, North Africa, and, later, in Europe. Nonetheless, the genus *Mus* (from the Sanskrit "mush," meaning to steal) is today distributed worldwide. The laboratory strains of mice used in biomedical research descend from the western European house mouse (*Mus domesticus*). The taxonomic designation *Mus musculus* actually comprises several interbreeding species. The albino and color mutants were developed at the beginning of 1900's and, since then, numerous strains became available for research. These include, among others, the BALB/c, DBA/2, and C3H strains and the Swiss mice. For more information on commonly used and genetically diverse inbred mouse strains see *e.g.* Paigen and Eppig (2000), Linder and Davisson (2004). Information on transgenesis techniques can be found *e.g.* in Bockamp et al. (2002), or Hafner and Müller (2004).

2.2 General anatomical features (see also Table 2)

The body length (head, thorax and abdomen in the rostral-caudal direction) and weight of an adult mouse average approximately 8-10 cm and 20-35 g, respectively. Mice have short hair, long naked tails, erect rounded ears, exophthalmic eyes, and pointed snouts with long vibrissae. There are several varieties of fur colors including albino, solid colors, and hooded patterns.

Mouse females have five pairs of mammary glands. Mammary tissue may extend up onto the lateral and dorsal regions of the trunk.

A large Harderian gland lies deep within the orbit. Its secretions contain a reddish-brown porphyrin pigment and increase under stressful conditions, appearing as 'red tears' around the eyes and nostrils.

The vertebral formula is 7 cervical, 13 thoracic, 6 lumbar, 4 sacral and 28 caudal, but there are variations between strains.

Dentition is monophyodont. Dental formula is reported in Table 2. As it is the general case for rodents, mouse incisors are lined with enamel only on their vestibular surface. The lingual surface is, instead, covered by a layer of dentine. The fact that the enamel is only found on one side of the tooth allows incisors to be perpetually honed against each other, creating a sharp chisel-like shape. Unlike human incisors, mouse (rodent) incisors have a yellowish/reddish pigmentation due to a higher presence of iron in the outer enamel layer. Iron incorporation in enamel is supposed to increase the tooth resistance to cracking and abrasion. Incisors have an open root (hypsodontic) and grow continuously. Molars are instead permanently rooted (brachiodontic).

The stomach is divided into two regions (Fig. 1B), both macroscopically and microscopically. The aglandular forestomach is lighter in color and thin walled, whereas the glandular part of the organ has a thicker, pinkish wall. The cecum is well developed and originates at the junction of the ileum and colon; its long axis is transversal and extends to the left side of the abdominal cavity. The liver (4 to 5% of the total body weight in adults) consists of four lobes. The heart is located along the midline and is surrounded by the lung lobes. The apex is close to the diaphragm.

There are 14 lymphocenters (mandibular, deep cervical, axillary, mediastinal, bronchial, coeliac, cranial and caudal mesenteric, lumbar, sacral, iliac, subiliac, superficial inguinal, and popliteal) which are comprised of 15-19 groups of lymph nodes (Kawashima, 1972).

The penis displays a well-developed os penis. The accessory male sex glands are the largest vesicular glands (seminal vesicles), the coagulating glands, the prostate (which has two pairs of lobes, dorsal and ventral), and the bulbourethral glands.

The ovaries and the uterus are close to the dorsal body wall. The uterus is bicorn (Table 2).

2.3 Unique anatomical/histological features

Circulatory system

The anatomical differences between the mouse and human heart have been extensively reviewed (Wessels and Sedmera, 2003). Between the interatrial septum and the interventricular septum the mouse heart possesses a small but thick atrioventricular septum, which is instead fibrous in humans. Conversely, the interventricular septum is not quite as massive and compact as in man. An additional remarkable feature is the different angle formed by the aortic valve with respect to the axis of the heart, having important impacts onto the physiology of circulation.

Differently from most mammals, the mouse pulmonary veins join together to form a single vessel that leaves the lung and opens into the dorsal wall of the left atrium. Also, mice have two anterior (cranial) caval veins that open into the right atrium, instead of a single one.

The anatomy of the coronary arteries is peculiar in several aspects. Mice possess a large septal coronary artery, which originates directly from the aortic sinus or as a branch of the right coronary artery, and runs along the interventricular groove, providing for the myocardial perfusion of the right ventricle and the interventricular septum. In addition, the mouse does not have an anterior coronary artery. Ligation the left coronary artery causes a myocardial

infarction with variable extension, which can affect the left ventricular anterolateral, posterior and apical walls, sparing the interventricular septum.

Respiratory apparatus

The trachea is composed of incomplete, "C"-shaped cartilages, whereas the left and right principal bronchi are supported by complete cartilaginous rings (Braun et al., 2004). The tracheal epithelium of the mouse is a single columnar layer. The majority of the tracheal epithelial cells are non-ciliated Clara-like cells; goblet cells are rare.

The anatomical differences between the mouse and human lungs have been extensively reviewed in the more general framework of the comparative use of different animal species to model chronic obstructive pulmonary disease in humans (Bland et al., 2007; Wright and Churg, 2008; Wright et al., 2008). Differences are mainly histological, although the pattern of lung lobulation and vascularization displays marked differences with that observed in man (Wright et al., 2008). Bronchial glands are absent. The number of non-ciliated bronchiolar cells in the small airways is ten-fold greater in mice (and rats) compared with humans; goblet cells are almost totally absent. Rodents, in general, do not normally have respiratory bronchioles, and mouse has no true alveoli at birth, with alveologenesis occurring during the first two postnatal weeks.

Immune system

As a general feature, the mouse immune system is developmentally delayed relative to humans (Holmdahl, 2004). Hematopoietic stem cells first appear at approximately eight days of gestation (Cumano and Godin, 2001). Intraembryonic blood cell development and emergence of the immune system occur in the postnatal period (Cumano et al., 2001). Differentiation of these cells to form lineage-restricted subpopulations of stem cells for the lymphoid and myeloid cell lineages has not been demonstrated before the tenth day, but mature lymphocytes are not found in the developing liver until day eighteen. Extramedullary

hematopoiesis is commonly observed in rodents as a normal component of the splenic red pulp. Spleen lymphopoiesis does not occur after birth under any experimental conditions tested, indicating that the bone marrow hematopoietic microenvironment is unique compared to that of other mammals (Paige et al., 1981). Extramedullary hematopoiesis occurs more frequently in young than in aged animals, in females than in males, and in mice than in rats. N mouse, it gives rise to erythroid and myeloid precursors, as well as multinucleated cells, most probably megakaryocytes (Suttie, 2006).

Genital apparatus

In males, the inguinal rings are open throughout life, allowing the testicles to be withdrawn into the abdomen.

The uterus has a single cervix at the junction of the body with the vagina.

Visual system

Mice have extensive periorbital venous sinuses behind the eye globe, a feature that makes easy the collection of relatively high quantities of blood. They display a well-identifiable Schlemm canal. The ciliary muscle, tapetum lucidum and lamina cribrosa are absent (Albrecht May, 2008). The retinal vascularization, optic disc and area centralis are pictured in Fig. 2B.

Auditory system

The mouse external auditory canal has a slight rostral curve as it approaches the tympanic membrane. The middle ear, as in all rodents, lacks mastoid air cells. The ossicular system is of a microtype (Lavender et al., 2011) and has restricted mobility: the malleus and incus are firmly joined by a synarthrosis, rather than by a freely mobile synovial joint like in humans.

3. Rat

3.1 Origin, general biology, and use in biomedical research

The taxonomy has been reported in 2.1. The common laboratory rat, the Norway rat *(Rattus norvegicus)* has a typical brown agouti coat color which is genetically dominant. It is believed

to have originated from ancestors living in central Asia, in the area between the Caspian Sea and the Baykal Lake. During the first half of the 18th century, these animals had followed human migrations to other parts of the world and displaced the wild black or roof rat *(Rattus rattus)*. Perhaps the most famous laboratory rat strain, the albino Wistar rat, derived from recessive stocks of animals transferred from Europe to USA in the late 1800's. Other widely diffused strains of rats were developed for research use in the first decades of 1900'. Among them are the Osborne-Mendel, the Long-Evans or hooded rat varieties, and the Sprague-Dawley. Today there are three main classes of rats that are employed in research; these include inbred strains, outbred stocks (known by generic names, *e.g.* Wistar, Sprague-Dawley, or Long-Evans, which indicate their historical origin), and mutants including the transgenic stocks (Franklin et al., 2006). Over three-hundred genetic loci associated with mutants and polymorphisms of various sorts have been described, and, recently, mutants such as the Big Blue rats have been produced using transgenic techniques for transgenesis assays (Erexson et al., 1998; Yamaguchi et al., 2008). The literature on laboratory rat is obviously very extensive, and there are numerous reference books and manuals that are in use in animal facilities to be consulted for information on the general biology, husbandry, and behavior of this species.

3.2 General anatomical features (see also Table 2)

The body length and weight of an adult rat are on average approximately 17 cm and 225-550 g, respectively. The superficial body features are similar to mouse. Likewise there is variability in colors of different stocks, strains, and mutants.

Rat females have six pairs of mammary glands. Mammary tissue has a widespread distribution on the thoracic and abdominal walls. The features of the Harderian gland are as in mouse.

The vertebral formula is 7 cervical, 12-13 thoracic, 6-7 lumbar, 3-4 sacral and 28 caudal.

Dentition is monophyodont. Dental formula is reported in Table 2. The gross features of incisors are identical to mice. Incisors have an open root (hypsodontic) and grow continuously. Molars are instead permanently rooted (brachiodontic).

The stomach is divided into two regions (Fig. 1C), both macroscopically and microscopically. The gross anatomy of the gastrointestinal tract, liver, and thoracic organs is very similar to that described for mice.

The number of lymphocenters is the same as in mice, but the groups of lymph nodes are 20-21 (Kawashima, 1972).

The os penis is well evident. The accessory male sex glands display the pattern described in mouse.

There is not a full accord on the classification of the rat uterus (see below).

3.3 Unique anatomical/histological features

Locomotor apparatus

The histology of the rat bone displays some significant differences when compared to that of humans (Hillier and Bell, 2007). The compact bone of the shaft in long bones is mainly formed by longitudinally oriented primary bone tissue, and Haversian systems are rare and scattered near the endosteal surface. Endosteal and periosteal circumferential lamellae are poorly developed, and there are diffused small areas of avascular and acellular bone (Singh et al., 1974). In aged rats (and mice) the degree of multicellular unit-based remodeling is reduced when compared to humans. In addition, although the rat/mouse bone shows estrogen dependency and thus may be useful for modeling osteoporosis, osteoblasts are not affected by long lasting sexual hormone deficiency (Kalu, 1991).

Digestive apparatus

Pharynx

The epiglottis rests against the soft palate and separates the nasal cavity from the oral cavity.

There are no tonsils in the oropharynx.

Circulatory system

Rats have two anterior caval veins. The right precava ends directly into the right atrium, while the left precava joins the azygous vein and, then, the caudal vena cava.

Respiratory system

Bronchial glands are present but concentrated in the upper portion of the trachea (Wright et al., 2008). Even when existing, the number of glands in rat and other small laboratory animals is markedly less than larger mammals, thus making most small-sized rodents a very poor translational model for human diseases such as chronic bronchitis (Wright et al., 2008). In the rat, the transition between pseudostratified and simple epithelium in proximal respiratory airways occurs at the hilum of the lung. Pulmonary lobules are highly immature at birth as alveoli are mainly formed in the first two weeks after birth.

Urinary apparatus

The kidney is unipapillate, having one papilla and one calyx, which enter the ureter directly. There are superficial nephrons that can be easily punctured using microscopic techniques. This characteristic makes rats attractive for kidney research, because other animals usually have less accessible nephrons. The urethra opens in the genital papilla near the base of the clitoris in females rather than in the vestibule of the vagina.

Reproductive system - female

According to most authors, the female rat has a bicorn bipartite uterus: the caudal part of the uterine body is undivided and the cervix protrudes into the vagina (Rendi et al., 2012). However, previous descriptions of the junction between the uterus and the vagina report the existence of two horns terminating independently into the single vagina through a separate cervix (Hamilton, 1947; Komárek, 2000). Therefore, differently from the doe, where the two

uteri are totally independent, there is an apparent fusion of the distal ends to form the uterine body.

Visual system

The ciliary muscle is absent. A vestigial tapetum has been described, but only in the Long-Evans hooded rat (Howell et al., 1982).

The optic nerve head forms a lamina-cribrosa like structure that is differently developed across strains: in the Brown Norway and in the Long Evans the lamina cribrosa is well-developed whereas in the Hooded and Wistar rat is only outlined (Johansson, 1987; Morrison et al., 1995; Balaratnasingam et al., 2014). Albino rats obviously have a non-pigmented retinal epithelium, but also an abnormal decussation of retinal ganglion cell axons at the optic chiasm, and a high susceptibility to light-induced photoreceptor apoptosis (Garcia-Ayuso et al., 2011). The retinal vascularization, optic disc and area centralis pictured in Fig. 2C.

Auditory system

The rat facial nerve exits the temporal bone more superficially and antero-rostrally than in humans. The ossicles are thinner than the human ones and are almost totally hidden in the epitympanic region. The stapedial artery runs between the stapes crura.

4. Hamster

4.1 Origin, general biology, and use in biomedical research

Hamsters belong to the order *Rodentia*, suborder *Myomorpha*, family *Cricetidae*. Several species of hamsters are used in biomedical research (Table 3). They have different behaviors as some, such as *C. griseus* and *C. cricetus* are quite aggressive and solitary, whereas others, *e.g. P. sungorus*, are tame and non-aggressive.

Approximately 90% of the hamsters used in research are of Syrian origin (Van Hoosier and Ladiges, 1984), descending from a few individuals captured in the 1930s (Clark, 1987). The

laboratory animal population is highly inbred, with only rare cross-breeding to wild living animals.

4.2 General anatomical features (see also Table 2)

The body length and weight of an adult Syrian hamster average approximately 14-19cm and 110-140 g, respectively. The hamsters' body is compact, with short legs and tail. Normally the mantle is reddish-gold, but color can range from albino to dark brown, with a grayish-white ventral abdomen. Hamsters have an excess loose skin. There is an average of seven pairs of mammary glands.

The vertebral formula is 7 cervical, 13 thoracic, 6 lumbar, 4 sacral, and 13-14 caudal. Dentition is monophyodont. Dental formula is reported in Table 2. Incisors are erupted at birth and grow continuously; the cuspidate molars are also erupted at birth but do not continue to grow.

Unlike other rodents, hamsters have a distinctly compartmentalized stomach (Fig. 1D) consisting of a forestomach (pregastric section) and glandular stomach (gastric pouch). The esophagus enters the non-glandular forestomach (also referred to as proventriculus). The forestomach, which is lined with a keratinized epithelium, is analogous to the rumen of ruminants and pseudoruminants. The cecum is well developed and divided into an apical and a basal portion by an external groove. The latter gives internally anchorage to a semilunar valve separating the two parts of the organ. Functionally, the hamster's alimentary canal can be considered the simplest example of a polygastric digestive system, as the microbial flora of the forestomach and the production and absorption of volatile fatty acids is analogous to that in polygastric animals. The liver is subdivided in four lobes.

The heart is located at the level of the 3^{th}-5^{th} thoracic ribs. Both the pulmonary and aortic valves have three cuspids. The orbital venous sinus is well developed, similar to mouse.

There are 12 lymphocenters (parotid, mandibular, deep cervical, axillary, mediastinal, dorsal thoracic, coeliac, cranial mesenteric, lumbar, iliac, superficial inguinal, and popliteal) that consist of 13 groups of lymph nodes (Kawashima, 1972).

The male os penis is well developed. Male accessory glands include the interior and exterior ampulla glands, the seminal vesicles, the coagulating glands, the prostate (three lobes), and the bulbourethral glands.

Ovaries are oval-shaped with a well-developed ovarian bursa and lay ventral to the kidneys; the uterus has two horns (Table 2).

4.3 Relevant embryological features

Wild-type hamsters have an extremely short pregnancy time of about 15-18 days. The relative immaturity of neonates makes this species an interesting model for reproductive studies. In addition, hamsters are widely used in cytogenetics as they have a low number of chromosomes (2N = 22), although the X and Y chromosomes of the Armenian hamster are of the same size and, thus, difficult to distinguish (Wood, 1998; Hendry, III et al., 2002; Reese et al., 2008).

4.4 Unique anatomical/histological features

Skin

Hamsters have a dorsal skinfold consisting of three layers of tissue, including the skin, the subcutis with the cutaneous muscle, and the retractor muscle. The loose attachment of the retractor muscle to the subcutis allows maintaining intact the primary vascular supply for microcirculation studies, in a specific experimental preparation referred to as the dorsal skinfold chamber (Menger et al., 2002).

Digestive apparatus

Syrian hamsters have a well-developed pair of cheek (buccal) pouches used to carry food and nesting material. The pouch is an invagination of oral mucosa that extends beneath the skin of

the buccal region. Its wall is composed of several layers (from the inside to the outside): *i.* the stratified squamous epithelium which is variably keratinized and continuous with that of the oral vestibule; *ii.* the *lamina propria* consisting of a very dense fibrous connective tissue layer devoid of papillae; *iii.* the muscle layer which is composed of striated skeletal muscles of varied thickness; *iv.* a loose subcutaneous fibrous connective tissue layer; and *v.* the cutis. Several studied converged to conclude that there are no blood or lymphatic vessels as well as lymphatic nodules and nerves in the pouch connective tissue and muscle layers (Fulton et al., 1946; Billingham et al., 1960; Lindenmann and Strauli, 1968). Subsequent observations led to the demonstration of a small population of lymphatic vessels (Bowen and Albertine, 1988). Nonetheless, the histology of the epithelium (skin-like epidermis), the reduced number of Langerhans cells, and the lack or paucity of lymphatic drainage allow to consider the pouches as an immune privileged district that can be used *e.g.* in tumor induction and transplantation studies (Chaimuangraj et al., 2003; Vairaktaris et al., 2008).

Respiratory system

Bronchial glands are almost totally absent in hamsters (Wright et al., 2008).

Immune system

The thymus at birth is at the same stage of development as that of an E16 mouse embryo The Syrian hamster displays several unique features of T cells and the immune system, *e.g.* skin grafts can be accepted from a different inbred strain differently from rats or mice. Additionally the genes of the major histocompatibility complex (MHC) are more closely related to humans compared to other rodents, and class 1 genes of the MHC and the molecules they code are functionally monomorphic, unlike other mammals (Holsapple et al., 2003).

Urinary apparatus

Kidneys are unipapillate and the renal pelvis is large and irregular in shape. The papilla is very long and reaches the ureter. This makes possible to collect the urine *in vivo* from single collecting tubules (Murray, 2012).

Visual system

The retinal vascularization and the localization of the optic disk and area centralis are pictured in Fig. 2D.

Hibernation and brown fat

Syrian hamsters are permissive hibernators, and during hibernation they remain sensitive to tactile and thermal stimulation (Tamura et al., 2005). Several studies on brown fat have been carried out in relation to the peculiar physiology of thermoregulation in these animals (Nicholls, 2001).

5. Gerbil

5.1 Origin, general biology, and use in biomedical research

Gerbils belong to the order *Rodentia*, suborder *Myomorpha*. Their subfamily (*Gerbillinae*) is part of the *Muridae* family, comprising more than one hundred species of rodents adapted to arid habitats, and originating from Africa, Asia and India. There is some confusion as regarding to the common names of the animals of the Gerbillinae subfamily that were once simply called desert rats. Other common names, often used as synonyms, are sand rat and jird although they should be referred to different species (Musser and Carleton, 2005).

The most widely diffuse laboratory gerbil is *Meriones unguiculatus*, the Mongolian gerbil, which is native to China and Mongolia. *M. unguiculatus* is characterized by a marked sexual dimorphism of, among others, the marking gland, an elliptical collection of sebaceous glands in the ventral aspect of the body, which is more prominent in males. This species develops spontaneous seizures and is thus used in epilepsy research (Loskota and Lomax, 1975; Ten et al., 1975; Loskota et al., 1974; Buckmaster et al., 2000; Kato et al., 2000; Mirzaeian and Ribak,

2000). It also tolerates much greater whole-body radiation exposures than other laboratory species (Suzuki et al., 1992).

Another species of research interest is *Psammomys obesus*, commonly known as fat sand rat. It is mostly found in North Africa and the Middle East, from Mauritania to the Arabian Peninsula (Kaiser et al., 2005a, b). Differently from most rodents, *P. obesus* is a diurnal animal, although the ambient temperature deeply influences its activity on the surface. Fat sand rats have very efficient kidneys with high water reabsorption capability, enabling them to survive the extreme heat and lack of water typical of the desert habitat (Jamison et al., 1979).

P. obesus is mostly used as a model for diabetes and obesity research as it easily becomes obese and acquires a diet-induced type 2 diabetes mellitus (Kaiser et al., 2012).

As a diurnal rodent, it has also been proposed as a preferable model of disorders related to circadian rhythms in the diurnal humans (Ashkenazy et al., 2009).

5.2 General anatomical features (see also Table 2)

The average body length and weight of adult gerbils are 11.5-14.5cm and about 87.5 (females)-100 g (males), respectively. The fur is usually reddish brown, but the mantle color can vary from tan to gray, with a gray or creamy white undercoat. The tail has a short fur at the base that becomes longer and bushy toward the tip. The sex of the adult animals is easy to differentiate as the males have a longer anogenital distance, prominent testicles, and a pigmented scrotum. Females have four pair of mammary bodies, two inguinal and two thoracic; the urethra is located outside the vagina.

The vertebral formula is 7 cervical, 13 thoracic, 6 lumbar, 4 sacral, 7 or more caudal.

Dentition is monophyodont, brachyodont (low-crowned) with anatomic roots that stop growing after they are fully erupted. Dental formula is reported in Table 2.

The stomach has similar features to that of the other *Myomorpha* considered here (Fig. 1F).

The cecum and colon are large, as in other rodents, but the granivorous gerbils tend to have

lower gut capacity and smaller cecum and colon that true rodent herbivores. The small intestine is longer than in more herbivorous species, with the small intestine being 48% and large intestine 40% of the total intestinal length (see Grant, 2014).

In Mongolian gerbils there are 14 lymphocenters (parotid, mandibular, deep cervical, axillary, mediastinal, coeliac, cranial and caudal mesenteric, lumbar, iliac, subiliac, superficial inguinal, sacral, and popliteal) which are comprised of 16 groups of lymph nodes (Kawashima, 1972).

5.3 Unique anatomical/histological features

Digestive apparatus

Teeth

Incisors are hypsodont and elodont (continuously growing without an anatomical root). Molars are brachydont with a well-defined root, anelodont, and terminate growth in mature subjects. Their anatomy has been described in details (Wasserman et al., 1970) as follows: the 3 molars of each quadrant consist of three, two, and one lobe respectively. The occlusal surfaces are flat and devoid of enamel. There are grooves on the buccal and lingual surfaces that run across entire height of the crown. On the buccal and lingual prominences of the crown lobes and on the interproximal surface, the enamel is covered by a thin layer of cementum which runs one-sixth up the height of the tooth. Within the grooves, a thick covering of globular-like cementum, which is continuous with the root covering, can be seen.

Circulatory system

The circle of Willis is incomplete in about 40% of the gerbils (Delbarre et al., 1988) and the collateral blood supply of the brain is limited when compared to rats or mice (Du et al., 2011; Martinez et al., 2012).This has important functional implications in experimental ligation of the internal carotid artery.

Immune system

The thymus is unusually large and persistent in adult gerbils (Wagner and Farrar, 1987).

Urinary apparatus

Differently from other rodents, the ratio of long-loop nephrons to short-loop nephrons is particularly high (Murayama et al., 1971). Ninety-six percent of the nephrons are long loop (Ichii et al., 2006).

Endocrine system

The adrenal glands are particularly developed and gerbils have one of the largest ratios of adrenal weight to body weight of all animals (Cullen et al., 1971).

Visual system

The retinal vascularization, optic disc and area centralis are pictured in Fig. 2E.The gerbil is active both during day and night and, differently from the nocturnal rats and mice, its retina is not exclusively rod-dominated. Compared with mice, gerbils possess a much higher proportion of cones to rods. Rods (peak sensitivity at 499-501 nm) represent about 87% of photoreceptors, the remaining cones being 12-14% of the total receptor population (Jacobs and Neitz, 1989). Gerbils have dichromatic, blue-green color discrimination capabilities with a net prevalence of green cones (95% and beyond), but their retina is also sensitive to UV light with a peak at 360 nm (Jacobs and Neitz, 1989; Govardovskii et al., 1992; Jacobs and Deegan, 1994; Szel et al., 1994). At birth the retina is highly immature in gerbils as formation of retinal layers occurs postnatally (Bytyqi and Layer, 2005).

Auditory system

A 3D model of the gerbil middle ear has recently been delivered in relation to the importance of this species in auditory research (Buytaert et al., 2011; Gea et al., 2010; Sichel et al., 1999). The tympanic bullae are very much developed, and gerbils can ear frequency peaks as high as 50kHz (Johnson and Marcotti, 2008). The pars flaccida of the tympanic membrane is circular and relatively large: it extends for about 10%-20% of the total surface, compared with only 2%-3% in humans (Von Unge et al., 2011). The ossicular system is of micro type, whereby the

handle of the malleus is fused to the tympanic ring (Decraemer et al., 2014; de La et al., 2010). The anterior mallear process extends from the anterior process of the malleus to the temporal bone, and is not seen in humans (Cohen et al., 1992).

6. Guinea pig

6.1 Origin, general biology, and use in biomedical research

Guinea pigs are *Rodentia* of the infraorder *Caviomorpha*. The domesticated guinea pig (*Cavia porcellus*), is related to the wild guinea pig (*Cavia aperea*) which is widely distributed throughout several Countries in South America. Guinea pigs were employed in biomedical research as early as in 1780, when Lavoisier used them to measure heat production (Tamballo and Fish, 2000). Among laboratory stocks are: the Hartley (or Dunkin-Hartley), an outbred shorthair albino; the NIH Outbred, a multi-colored guinea pig; and the hairless, euthymic guinea pig. Only two inbred strains are readily available today: Strain 2 and Strain 13. The guinea pig is not considered closely related to mice and rats but rather to chinchillas and porcupines (North, 1999).

6.2 General anatomical features (see also Table 2)

The body length and weight of the adult animals range from 20-50 cm, and 850-1,000 g, respectively. Guinea pigs are stout and short-legged. According to breeds, the mantle comes in several colors and color combinations, including black, tan, cream, brown, and white. The female has a single pair of inguinal mammary glands.

The vertebral formula is 7 cervical, 13-14 thoracic, 6 lumbar, 2-3 sacral and 6 caudal. Dentition is monophyodont. Dental formula is reported in Table 2.

Guinea pigs are hindgut fermenters with a monogastric glandular stomach (Fig. 2F), and a large cecum and colon. The large sac-like cecum, which holds up to 44-65% of the total gastrointestinal content, is thin-walled and lies between the small and large intestine, in the

most caudal part of the ventral abdomen. The proximal colon represents approximately one-third of the total colon length.

The heart is located mostly on the midline and approximately 1 cm cranial to the xiphoid process.

The most important lymph nodes of the guinea pig are the maxillary, cervical, axillary, cubital, inguinal, mediastinal, mesenteric, and iliac (Breazile and Brown, 1976).

An os penis is found within the dorsal surface of the entire length of the glans. Among male accessory sex glands (vesicular glands, prostate, coagulating glands, and bulbourethral glands), the vesicular glands (paired) are the most developed and may reach 1 cm in length and 6-9 mm in diameter.

6.3 Relevant embryological features

Gestation length varies inversely with litter size and pregnancy lasts between 59 and 72 days (68 days as an average). Guinea pigs are among the few precocial laboratory animals: this has numerous implications in relation to the maturation of the nervous system, particularly of motor circuitries.

6.4 Unique anatomical/histological features

Digestive apparatus

Teeth

Giunea pigs are monophydontic, and all their twenty teeth are hypsodontic, *i.e.* they are open rooted and erupt continuously (Hargaden and Singer, 2012). The incisors are covered by enamel that forms a pseudo-crown, and are thus white and not yellowish/reddish as observed in other rodents. Uniquely to other mammals, these teeth receive a parasympathetic innervation (Segade and Quintanilla, 1990). Together with the molars, guinea pig incisors display an unconventional distribution of Ruffini's mechanoreceptor endings in periodontal tissues (Jayawardena et al., 2002).

Pharynx

The soft palate is well developed and reaches the base of the tongue to which it connects by the palatoglossal arches. Therefore, the intrapharyngeal ostium is quite small. The oropharynx and the nasopharynx communicate via the palatal ostium, a hole in the soft palate (Hargaden and Singer, 2012).

Stomach

Monogastric guinea pigs display a remarkable extension of the mucosal area occupied by the fundic glands (Fig. 2F). The lesser curvature of the stomach is small and forms an angle with the esophagus referred to as the angular notch. This differs from most other mammals where the angular notch is seen along the lesser curvature, and is used to draw the limit of the body of the stomach with the pyloric region.

Intestine

The small intestine is not divided in three sections (duodenum, jejunum, ileum) as in most mammals. Lymphoid tissue (Peyer patches) in the lamina propria are found throughout its length.

Circulatory system

There are significant anatomical differences in the guinea pig circulatory system in comparison to other laboratory mammals and humans (Stump and Shively, 1976; Shively and Stump, 1975; Shively and Stump, 1974). The main issues are the following:

- Coronary arteries are not terminal vessels as they display an extensive degree of collateralization. Thus their occlusion is unlikely to produce a myocardial infarction in comparison to rats or pigs (Brewer and Cruise, 1994).
- The bronchoesophageal artery originates from the right costocervical artery, the right internal thoracic artery, or the brachiocephalic trunk.

- The internal carotid arteries are small and play a marginal role in the cerebral blood supply, which mainly derives from the internal ophthalmic arteries.
- The pulmonary trunk and the pulmonary arteries display a thick tunica muscularis, which is also present in the form of isolated swellings within the pulmonary veins.
- Lung capillaries are extremely variable in size from the periphery to the center of pulmonary lobules (Sekhon et al., 1995).

Blood

The presence of Kurloff (Foa-Kurloff) cells is unique to guinea pigs. These cells are mononuclear leukocytes with natural killer activity that are found in the circulating blood, splenic sinusoids, bone marrow, and thymus (Pouliot et al., 1996; Landemore et al., 1993).

Respiratory system

The guinea pig well recapitulates the histology of the human tracheal epithelium and subsegmental bronchi, although bronchial glands are irregularly distributed. Pulmonary alveoli are well developed at birth and there is a limited alveologenesis with age (Wright et al., 2008).

Urinary apparatus

The kidney parenchyma, at the junction between the single papilla and the renal pelvis, contains atypical "pacemaker" cells. These are smooth muscle cells capable of generating pacemaker potentials in the proximal renal pelvis. The latter also contains cells similar to interstitial cells of Cajal (Klemm et al., 1999).

Nervous system

Together with the *Macacus rhesus* and the spiny mice (Genus *Acomys*) among laboratory species, guinea pigs are precocial mammals. Timing of the brain and spinal cord development have been studied by different approaches focused *e.g.* on glial cell multiplication and myelination (Dobbing and Sands, 1970), or microtubule assembly (Lennon et al., 1980).

Among brain areas, the anatomy of the cerebellum has been the focus of early comparative investigations (Hargaden and Singer, 2012), followed by more recent immunocytochemical studies on the expression of several neurochemical markers, including *e.g.* excitatory amino-acids , somatostatin (Taber-Pierce et al., 1985), zebrin II (Larouche et al., 2003), or S-100 (Haglid et al., 1977). Differences in apoptosis of cerebellar granule cells in relation to a different timing of development have also been described in comparison with rabbit and mouse (Lossi et al., 2002; Lossi and Gambino, 2008). A neuroinformatic resource that combines neuroscience, evolutionary science, statistical modeling and computer science is available at http://www.translatingtime.net/home for proper comparison of neurodevelopmental data across laboratory species (Clancy et al., 2007).

As in most mammals, the respiratory activity is controlled by two groups of neurons: a dorsal respiratory group (DRG) and a ventral respiratory group (VRG) both located in the tegmentum of the medulla oblongata. However, differently from rats, the DRG is located ventrally to the tractus solitarius (Richerson and Getting, 1992).

Visual system

The guinea pig retina (paurangiotic) is almost completely devoid of blood vessels (Fig. 2F), the existing ones being minute and restricted to the direct neighborhood of the optic nerve head (Rodriguez-Ramos and Dubielzig, 2013). Guinea pigs, differently from mouse, rat and gerbil, have both A- and B-type retinal horizontal cells (Peichl and Gonzalez-Soriano, 1994).

Auditory system

Guinea pigs have large tympanic bullae and the internal ear is easily accessible. Although these animals are widely used in auditory research, there are several discrepancies in the anatomical description of their middle and inner ear (Hargaden and Singer, 2012). The main peculiarities are the following:

- The external auditory canal has a foramen in its antero-inferior aspect, similar to the foramen typanicum seen in young children.
- The tympanic membrane only has the pars tensa.
- The middle ear is divided into a ventral bulla and a dorsal epitympanum by the projection of the cochlea.
- The epitympanum is compressed latero-laterally and contains a fused malleo-incudal complex.
- There is a simplified air cell system of four large cells.
- The oval window is orientated vertically while the round window sits horizontally.
- The auditory tube is totally cartilaginous.

7. Rabbit

7.1 Origin, general biology, and use in biomedical research

Rabbits belong to the order of *Lagomorpha* (also referred to as *Duplicidentata* in the past). The European rabbit, *Oryctolagus cuniculus* is widely used in research, and rabbits are likely to be the largest laboratory animal with commonly available inbred strains (Burkholder et al., 2012). The most commonly used breeds are the New Zealand White (albino), the American Dutch, and the Californian. The American Dutch rabbit is less than half the size of the New Zealand White. The literature on rabbit biology, physiology and behavior is very extensive and readers are encouraged to consult it for specific descriptions of features of comparative interest (Brewer, 2006; Burkholder et al., 2012).

7.2 General anatomical features

The body length and weight of adult average-size breeds, such as those used in research, is 3.5-4.5 kg and 48 cm, respectively. The color of the mantle varies in different breeds, being completely white in the New Zealand White, or with characteristic black and white patterns in the American Dutch and the Californian rabbits.

The rabbit skin is very delicate and quite thin, and is exceptionally prone to tearing, with the exception of that of the intact males. Females have a characteristic skin fold, the dewlap, in the ventral part of the neck. There are four or five pairs of mammary glands. Male rabbits lack nipples. Differentiating males from females can be difficult, as the anogenital distance is the same in both sexes.

There are no palmar/plantar cushions; instead the distal ends of the limbs are thickly furred to protect the palmar/plantar surfaces that support the body.

The vertebral formula is 7 cervical, 12-13 thoracic, 6-7 lumbar, 4 sacral, and 14-16 caudal.

Rabbits are diphyodont, this being one of the distinctive features of lagomorphs in comparison to rodents. However, in lagomorphs, the deciduous teeth are rarely seen as they are generally shed before birth or shortly thereafter. The white enamel encases the incisors at both the vestibular and lingual surfaces.

The stomach is fully glandular, with a wide area of the fundus occupied by the cardial glands (Fig. 1 G). The small intestine of rabbits has an extremely reduced lumen. The ileum ends at a T-shaped junction with the cecum and large intestine, in a section called the sacculus rotundus (see below). The cecum is thin-walled but extremely large and distensible. It coils upon itself three times within the abdominal cavity, and displays well visible tenias and haustra.

The cardiovascular system of rabbits is unique (see below). The heart is small relative to total body size, comprising only 0.3% of the total body weight.

Rabbits are obligate nasal breathers. The trachea is narrow relative to body size. The thoracic cavity is small in comparison with the large abdominal cavity.

The testicles are located within hairless scrotal sacs, cranial to the penis. The inguinal canals remain open throughout life. Male accessory glands include the seminal vesicles, the vesicular

gland (cranial prostate), the prostate, the paraprostatic glands, and a bilobed bulbo-urethral gland.

Ovaries are very elongated in the rostro-caudal direction, and are relatively far from the kidneys (about 2-2.5 cm). The uterus is duplex.

7.3 Relevant embryological features

The doe ovulates about ten hours after mating, and gestation lasts 30-32 days. Therefore, rabbits are particularly suitable for studies where precise timing of embryonic development is required. Similarly to humans, the placenta is hemochorial.

7.4 Unique anatomical/histological features

Locomotor apparatus

The skeleton represents about 8% of the total body weight and is, therefore, quite fragile in comparisons of other animals of similar size, *e.g.* the cat (Brewer, 2006), making *O. cuniculus* the model of choice for bone fracture (Reifenrath et al., 2014) and osteoarthritis studies (Laverty et al., 2010). Nonetheless, rabbit long bones are histologically much different from their human counterparts (Wang et al., 1998), as the mature bones displays vascular canals of osteons running parallel to their long axis resembling the structure of the primary bone, rather than of the mature bone in humans (Martiniakova et al., 2005).

Digestive apparatus

Teeth

Differently from *Rodentia*, *Lagomorpha* have two pairs of upper incisors. The upper and lower incisors grow about 10-13 cm/year. The permanent teeth grow until 3-5 weeks. Rabbits are hypsodont and their teeth are devoid of a true root.

Salivary glands

Besides the three major (extramural) salivary glands found in mammals (parotid, mandibular and sublingual), rabbits also have a zygomatic gland (Gargiulo et al., 1996).

Esophagus

The mucosa is devoid of glands and the tunica muscularis is formed by three layers of semi-involuntary striated muscles that extend all along the course of the organ.

Intestine

The rabbit intestine has many peculiar anatomical features that are primarily related to the biology and herbivore feeding habits of this species, as the rabbit is a monogastric hindgut fermenter (Burkholder et al., 2012; Snipes et al., 1982). The caudal flexure of the duodenum is long and coiled; it is homologous to the transverse part of the duodenum in other mammals. The sacculus rotundus is peculiar to the rabbit: it is an enlargement of the large intestine at the ileo-cecal junction. The sacculus is largest and most prominent organ of the abdominal cavity containing about 40% of the ingesta. Its wall is infiltrated by abundant lymphoid tissue that is often referred to as the ileocecal tonsil.

A particular area of the colon is the fusus coli, a section of the proximal colon that operates as a pacemaker area for the two types of feces produced by rabbits, and functionally separates the ascending colon from the transverse and descending portions (Ruckebusch and Fioramonti, 1976).

The bile duct and the pancreatic duct enter the duodenum separately.

Circulatory system

Heart

Both the right and left atrioventricular valves are bicuspid. Histologically, the sinoatrial (SA) node is well-defined and much developed in relation to the heart size, whereas the atrioventricular node and the His bundle are relatively small (James, 1967; James and Sherf, 1971). The SA node has a very large percentage of Purkinje cells that are very easily identifiable due to their long cylindrical shape, and, indeed, the SA was first discovered in rabbits (Bleeker et al., 1980). There is little or no connective tissue intermixed to the Purkinje

cells, which are, instead, separated by very wide clefts. These features make the rabbit the species of choice to study the heart conduction system.

Blood vessels

In general terms, rabbit blood vessels are thin-walled and prone to collapse and hematoma formation upon puncture (Burkholder et al., 2012).

The pulmonary artery is an exception, as it consists of a very thick muscular wall that makes the rabbit naturally prone to pulmonary hypertension. The internal carotid artery is relatively small although it is the main vessel serving the brain.

Rabbits have a left and right cranial vena cava, and, as a result, the coronary sinus is very large (Pariaut, 2009). Differently from most mammals, the external jugular vein provides the main route for venous drainage from the head. There is a lack of anastomoses between the external and internal jugular veins. This is important because ligation or thrombosis of the external jugular vein can lead to temporary exophthalmia.

Blood

Rabbit neutrophils contains eosinophilic granules and are thus sometimes called amphophils, pseudoeosinophils or heterophils (Brown et al., 1983). Eosinophils are larger than the neutrophils.

Respiratory system

Bronchial glands are absent (Wright et al., 2008).

Urinary apparatus

Rabbits have a unipapillate kidney in which one papilla and one calyx enter directly the renal pelvis (Dwyer et al., 2000). The vascularization of the medulla displays some specific histological features in comparison to rat and mouse (Kaissling, 1977; Kaissling and Kriz, 1979). It is also noticeable that the renal tubules can be isolated with an intact basement membrane, a fact that is particularly useful in functional studies (Brewer, 2006). Thirty-four

percent of the loops of Henle are of the short type (Kaissling and Kriz, 1979), differently from rat, mouse, and humans.

Respiratory apparatus

The spatial contiguity of the soft palate and the large epiglottis leads to a direct communication of the nasopharynx with the larynx and the trachea, making the rabbit an obligate nose-breather, a feature of relevance when attempting to intubate the animal (Brewer, 2006).

Bronchial glands are absent, and the rabbit lungs are devoid of respiratory bronchioles (Wright et al., 2008). The relevance of rabbit in the study of asthma has been specifically reviewed elsewhere (Keir and Page, 2008).

Genital apparatus – female

The microscopic anatomy of the ovary is very peculiar as the interstitial tissue occupies about 4/5 of the gonad. It forms a very compact tissue between the vascular zone and a thin cortex containing the follicles. There are two uteri, each of which opens into the vagina through a separate cervix.

Nervous system

The rabbit cerebellum has prominent paraflocculi (Marani and Voogd, 1979). The paraflocculus, a small lobule of the cerebellar hemisphere, is separated from the flocculus, but linked to the pyramis and uvula. The flocculus has been extensively studied as a part of the flocculo-nodular lobe of the cerebellum which plays a major role in vestibulo-ocular reflexes and sensory/sensorimotor integration for the stabilization of the image on the retina (Voogd et al., 1996).

Visual system

The rabbit eye is compressed in the antero-posterior axis, in contrast to the human eye which is relatively spherical. Structures of the eye that are not present in humans include a well-

developed retractor bulbi muscle, and the third-eyelid gland (Harder's gland), an acino-tubular gland that lies in the ventro-nasal quadrant of the orbit. The lipid secretion of the gland stabilizes the tear film, and rabbits are thus able to resist blinking for long intervals.
Review of published literature has shown that the rabbit lacrimal system is more closely related to that of humans than in rats or mice (Schechter et al., 2010), and recent work has described the anatomy and structural features of the lacrimal duct system (Ding et al., 2010).
Unique to the rabbit is the aqueous humor drainage system. The aqueous humor reaches a series of trabecular veins, which are located external to the corneo-scleral trabeculae and are the homologous of the Schlemm's canal in humans. These collector canals are linked to deep scleral channels which cross the sclera to connect with the episcleral and conjunctival veins.
The rabbit corneal epithelium is approximately 30-40 μm thick, therefore thinner than in man (Labbe et al., 2006). It consists of a row of columnar basal cells beneath two rows of polygonal and up to six rows of wing shaped and squamous cells on the external surface. The cornea is devoid of a significant Bowman's membrane. Differently from rats and mice, the nuclei of rabbit corneal keratocytes are visible as hyper-reflective structures. Thus, their density can be easily evaluated. Endothelial cell density is higher than in rats and mice, and the endothelium regenerates in response to injury loss.
The ciliary body is small and comparatively flat as the result of a limited development of the ciliary muscle.
The choroid is well developed. It has an arrangement similar to that in humans and is devoid of a tapetum. The retinal pigment epithelium is irregular in size and arrangement, unlike the regular hexagonal configuration in humans.
The retina is merangiotic (Fig. 2G) and only part of the inner retina is vascularized by the retinal vessels, which are confined to a broad horizontal band coincident with the area of dispersion of the myelinated nerve fibers (Agrawal et al., 2007). The larger of these vessels

are readily visible (De Schaepdrijver et al., 1989). The remainder of the rabbit retina is avascular. This is in contrast with the euangiotic/holangiotic retina seen in primates and rodents, where the retina is supplied by the central retinal artery or the cilio-retinic arteries. Rabbits show a poorly developed lamina cribrosa and the optic nerve head contains neuronal tissue and astrocytes in addition to oligodendroglia (Albrecht May, 2008).

There is not a true fovea centralis, but a visual streak consisting of two broad white bands of opaque nerve fibers, the medullary rays, that extend nasally and temporally in the horizontal plane (Fig. 2G).

Photoreceptors are comparatively extremely long and thin. The rabbit has only blue and green cones and a unique bipolar and outer plexiform layer arrangement (Pan and Massey, 2007).

Auditory system

The tympanic bulla is relatively large and continues dorsally into the osseous external auditory canal which is longer than in most other mammals (Burkholder et al., 2012).

8. Pig

8.1 Origin, general biology, and use in biomedical research

Pigs belong to the order of *Artiodactyla*, family of *Suidae*. They are very similar anatomically and physiologically to humans and thus widely used in translational research (Bollen et al., 2010; Kobayashi et al., 2012). Domestic pigs originate from the Eurasian wild boar *Sus scrofa* (Giuffra et al., 2000). Through selection, numerous breeds have subsequently been developed, and those existing today are relatively recent. The Landrace, one of the commonest domesticated breeds, is considered to have derived from the Local Celtic swine in the two past centuries following crosses with Chinese and English breeds in the early 1800s. The Yorkshire or Large White breed is native to England (Groenen et al., 2012).

8.2 General anatomical features (see also Table 2)

Pigs employed in biomedical research comprise several domestic breeds, *e.g.* Landrace, Duroc, Large White, Yorkshire and Hampshire, and the miniature swine. The differences between domestic farm breeds and miniature breeds are related to their growth rate and size at sexual maturity rather than actual anatomic differences in organs and their structure. In general, domestic breeds grow from 1–2 kg at birth to more than 100 kg at 4 months of age, reaching a body length up to 125 cm. The Hanford, Yucatan, Yucatan micro, Sinclair, and Göttingen are the most common miniature breeds (from largest to smallest). These miniature swine weigh 0.5–1 kg at birth and grow to 7–20 kg in 4 months according to breed.

The color of the skin and the presence of hairs vary considerably among breeds both in domestic ad miniature pigs. There are in average, six to seven pair of mammary glands.

The vertebral formula is 7 cervical, 14-15 thoracic, 6-7 lumbar, 4 sacral, and 20-23 caudal.

The pig has a complete, diphyodont dentition; the deciduous dental formula is 3/3, I/I, 4/4. The canine teeth (fangs) grow continuously throughout life.

The stomach is typical of monogastric species, except for a diverticulum of the fundus (Fig. 1H) and a torus pyloricus, at the level of pylorus. The small intestine has a longer duodenum and a very short ileum compared to humans and non-human primates. The large intestine of the pig is anatomically very different from that of human, laboratory rodents and rabbits. The cecum is a well-developed cylindrical organ that lies transversally in the abdomen, with the basis on the left side. The ascending colon, in the left lateral abdominal region, is arranged in a series of centrifugal and centripetal coils, referred to as the spiral colon.

The heart does not display significant variations compared to other mammals, its size in Hanford sexually mature minipigs is analogous to that of the human heart. The coronary blood supply is almost identical to that of humans.

There are 18 lymphocenters (parotid, mandibular, retropharyngeal, superficial and deep cervical, axillary, dorsal and ventral thoracic, mediastinal, bronchial, coeliac, cranial and

caudal mesenteric, lumbar, popliteal, superficial and deep inguinal, ileosacral) which are comprised of 48 groups of lymph nodes.

The male penis is of the fibromuscular type, almost devoid of erectile tissue. Accessory sex glands include prominent vesicular glands, a small prostate gland, and the bulbourethral glands.

The ovary has a very irregular surface due to the presence of multiples follicles. The uterus has two horns (Table 2) that form loops intermingled with those of the small intestine.

8.3 Relevant embryological features

The pig has diffuse epitheliochorial placentation and transplacental transport of substances is very similar to that of humans.

8.4 Unique anatomical/histological features

Skin

Swine has a fixed skin with a tight attachment to the subcutaneous tissues with a comparatively reduced vasculature (Swindle et al., 2012).

Locomotor apparatus

Some differences in the long bone architecture have been described (Hillier and Bell, 2007). Femora of mature pigs consist primarily of plexiform bone with the dense Haversian tissue located at the posterior portion of the bone, whereas the cortical bone of immature pig femora consists of layers of lamellar bone alternating with primary bone tissue containing only a few osteons.

In pig muscles, there is a predominance of type II fibers with a lesser number of type IIA and IIC. Type grouping in the pig consists of islets of slow-twitch type I fibers surrounded by type IIA and, more peripherally, type IIB fast-twitch fibers (Swindle et al., 2012). Thus, the pig muscle has a fiber composition closer to that of humans in comparison to mice, rats, and rabbits, as these are species where the type IIB predominates.

Circulatory system

The major anatomic variation from other mammalian species is the presence of the large left azygos (hemiazygos) vein entering the coronary sinus. The external jugular vein is relatively large, but not as superficial as in other common laboratory animals.

The conduction system is made of large numbers of easily identified Purkinje cells intermingled with numerous adrenergic and cholinergic fibers in the atrioventricular node and left and right bundle branches. This makes the conduction system easily identifiable in comparison with mammals other than the rabbit (Michel and Gutte, 1966; Bytzer, 1979; Toshimori et al., 1988).

Immune system

The pig lymph nodes have a unique architecture in comparison to the other species considered here and to humans, that is, the cortical and medullar subdivisions of the parenchyma are intermingled, with most of the outer lymph node surface being occupied by the medullary, and the cortex lying deep into the organ with the exception of the hilum (Fig. 3; Merighi et al. 1986). An inverted flux of the lymph inside the lymph node is accompanied to this arrangement.

Digestive system

Unlike most domestic animals, Peyer's patches occur in a continuous band along much of the length of the small and large intestine. Histologically, the liver pattern presents a markedly defined lobulation, and, unlike rodents, pigs have well-defined acinar structures with clear portal triads, similarly to humans.

Urinary system

The pig has a lobated, multipapillate kidney with true calices, as in man. The avascular plane of the kidney is transverse in swine, differently from humans, and this has important

implications in renal surgery. The sympathetic innervation of the pig urethral muscle arises from both lumbar and sacral sympathetic trunk ganglia (Botti et al., 2014).

Brain

The anatomy of the pig brain is comparable to that of humans in its macroscopic aspects, myelination, growth and development (Jelsing et al., 2006b), and a considerable body of evidence indicates that it resembles the primate brain more than the rodent brain does, specifically in relation to the localization of cortical sulci and giri, and to the shape and total number of neocortical neurons (Lind et al., 2007). Although the macroscopic anatomy of the pig brain is well known, only a few quite old studies exist on its histology. They have for the most addressed the overall structure and cellular organization of the neocortex. After functional studies, it has been shown that the somatosensory cortex has a somatototopic organization and connectivity with the thalamus very similar to that of humans (Jelsing et al., 2006a). Also, the striatum is well developed and, like that of primates and differently from most mammals including rodents and rabbit, the pig is the only laboratory species in which it is individualized into a distinct caudate and putamen (Felix et al., 1999).

In contrast to humans, there are two middle cerebral arteries for each hemisphere both originating from the internal carotid artery, one coursing laterally and the other rostrally over the olfactory tract (Imai et al., 2006).

Visual system

The porcine retina is holangiotic (Fig. 2H) and the major retinal venules lie centrally in the optic disc (De Schaepdrijver et al., 1989). The lamina cribrosa is very strong and completely embeds the retinal blood vessels (Czajka et al., 2004). Cones are concentrated along the horizontal streak that lies above the optic disk (Fig. 2H).

9. Conclusion

The choice of the best suited animal model for translational research is of primary importance to maximize the possibility of a successful transfer of results to human pre-clinical research. Although functional features are as well important, there are numerous anatomical singularities that make a single species suitable or unsuitable to the purpose. An in-depth knowledge of these features is surely useful in directing the experimenter's choice towards the best options available.

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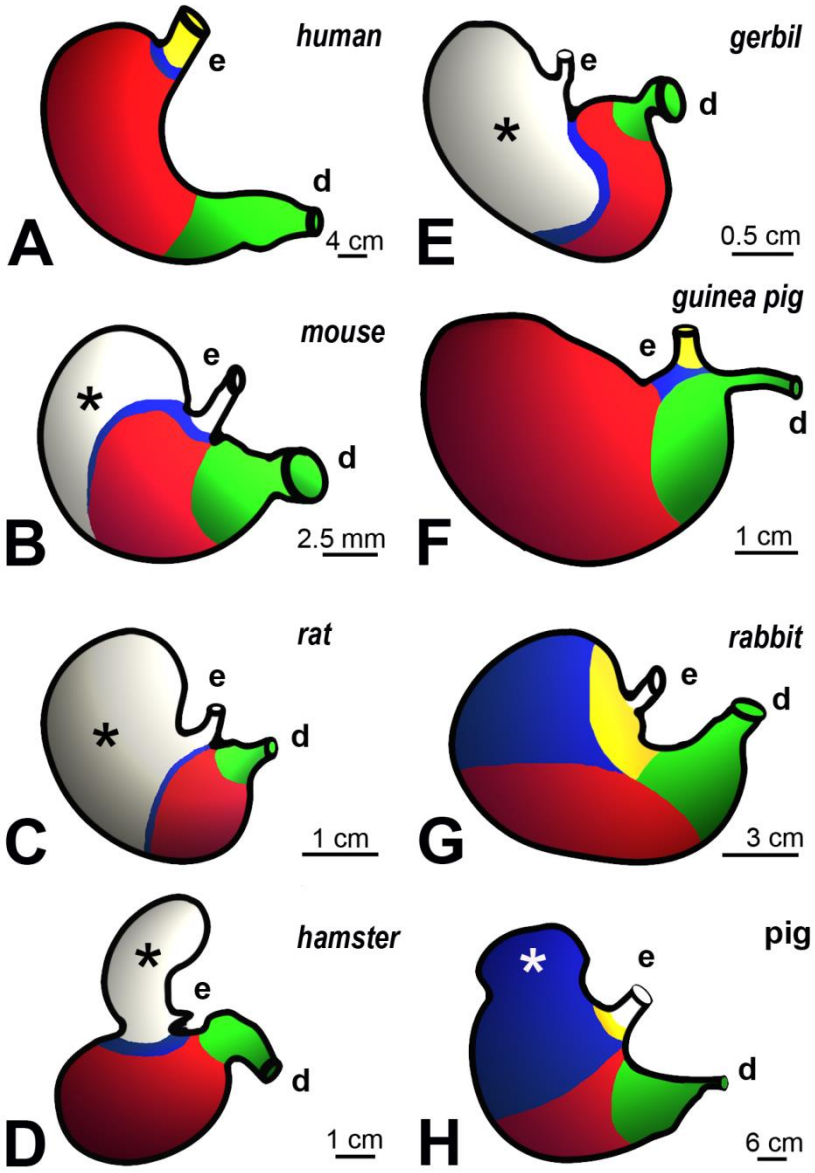

Figure 1: Schematic drawings illustrating the comparative anatomy of the stomach and the distribution of the gastric glands. The aglandular mucosa is gray; the areas occupied by the cardial, fundic (gastric glands proper), and pyloric glands are blue, red, and green, respectively. The areas esophageal glands are inWith the exception of Guinea pig (F), rodents (B-D) have an aglandural part of the stomach that is also referred to as the proventriculus (D – hamster) or as the proventricular part of the stomach (asterisk). In pig, there is a gastric diverticulus (asterisk) that is homologous to the proventriculus but contains cardial glands in the mucosa. Note the presence of an area with esophageal glands (yellow) in rabbit (G), and pig (H). Abbreviations: d = origin of duodenum; e = termination of esophagus. The greater curvature is ventral left, the lesser curvature is dorsal right.

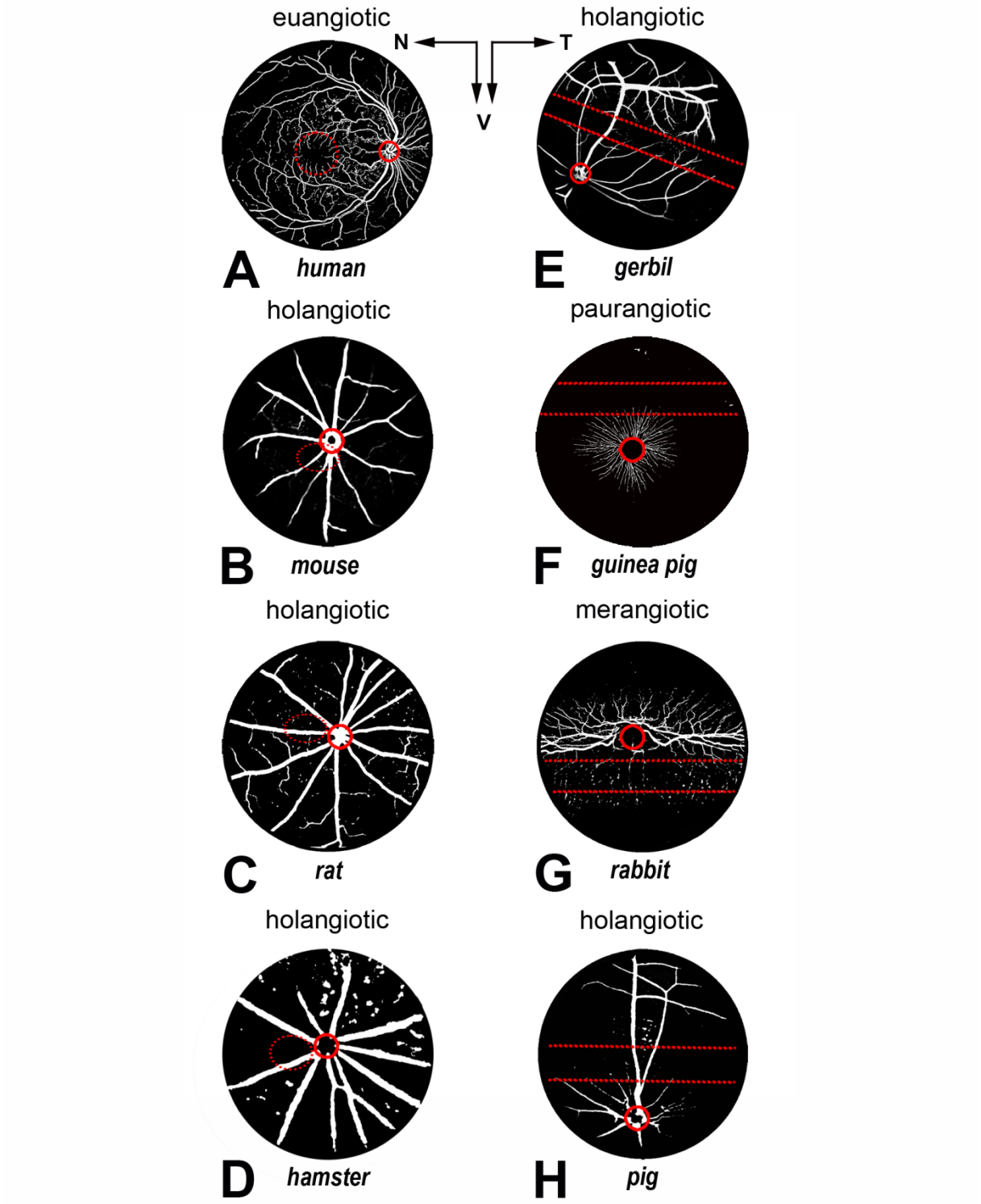

Figure 2: Semi-schematic drawings illustrating the comparative anatomy of the retinal vasculature and the distribution of retinal specializations (fovea, area centralis, and visual streak). Drawings have been obtained from original fluorangiographies. The area of the optic disc is indicated by a red circle. The retinal vasculature varies significantly between primates and other mammals (see Lutty et al. 2012 for further information). When the retina is supplied by a central retinal artery, the pattern of vascularization is referred to as euangiotic as it occurs in humans (A) and primates. In the rodent (B-E) and pig (H) holagiotic retinas the retinal blood vessels derive instead from the cilio-retinic arteries, whereas in the guinea pig paurangiotic retina (F) there are only very small vessels around the optic disc. The rabbit retina (G) is merangiotic: blood vessels are present only in a small

part of the retina, extending in a horizontal direction to form bands on either side of the optic disc. The merangiotic pattern is considered by some authors to be part of a larger group, the angiotic retinas, where only a part of the retina is vascularized.
Retinal specializations are indicated by dotted lines. They are related to visual acuity, and thus to a high density of the cone photoreceptors. The human retina (A) displays a true fovea that is located in correspondence to the optic axis of the eye. The area centralis and the visual streak in several laboratory mammals can be defined as areas of higher density of retinal cells after cresyl violet staining. In most rodents and in pig, it is possible to identify an area centralis (B-D) or a visual streak (F-H), also referred to as horizontal streak in rabbit, on the basis of the density of the cells in the retinal ganglion cell layer (but see text for the unique features of cone distribution in mouse). The strip-shaped area centralis in gerbil (E) represents the distribution of horizontal cells. Further details on retinal specialization maps can be found at http://retinalmaps.com.au//.

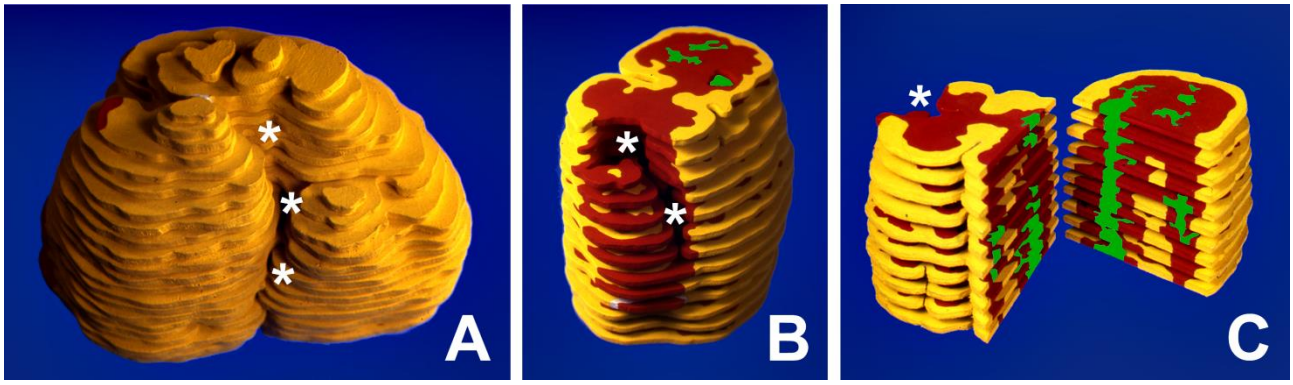

Figure 3: 3D models of the pig lymph nodes. Medulla-like tissue is yellow, cortex-like tissue is red. Lymph vessels are dark green. Lymph nodes in pigs derive from the fusion of smaller units that are independent during embryonic life. Each unit consists of a spheroid, with medulla-like tissue at periphery and cortex-like tissue at center. The cortex-like tissue reaches the periphery at a restricted area where the lymph vessels enter or exit the node (see Merighi et al. 1986 for further details). A: a node showing a deep notch (asterisks) resembling a hilum that is fully lined with medulla-like tissue. B-C: A node showing a hilum-like depression (asterisk) that is occupied by cortex-like tissue (red). In C the model has been opened to display the arrangement of the cortex- and medulla-like portions of the parenchyma. The asterisk in C indicates the notch marked by the asterisk in B.

Table 1

Main fields of use		Mouse	Rat	Hamster	Gerbil	Guinea pig	Rabbit	Pig
Anatomy and physiology		Basic research (general)		Urinary apparatus (pathology)	Brain circulation	Embryogenesis Teratogenicity	Basic research	Biology of reproduction Circulatory system (pathology)
Applied pharmacology Development of biomedical devices		General use				Vitamin C deficiency		General use Xenotransplantation
Pathology	*Cancer and cancerogenesis*	General use		Oral cavity tumors Pancreatic tumors	Radiation research		General use	
	Toxicology	General use			General use		General use	General use
	Neurological disturbances, neuropathology and neurodegeneration	General use		Epileptic syndrome	Audiometry Vascular pathology	Audiometry	Neurological disturbances	
	Endocrinology and endocrine pathologies	General use		Diabetes	Adrenal glands			Diabetes
	Genetic pathologies	General use		Muscular dystrophy		Asthma	Hypertrophic cardiomyopathy	Cystic fibrosis
	Others	General use		Atherosclerosis Thrombosis Caries		Infectious diseases	Atherosclerosis Infectious diseases	Cutaneous regeneration
Surgery		General use (microsurgery)				Eye (hypermetropia)	Eye	General use

Table legend: Summary of the utilization of different mammalian species in current biomedical research

Table 2

		Humans	Mouse	Rat	Hamster	Gerbil	Guinea pig	Rabbit	Pig
Skeleton	***Clavicle***	Present	Present	Present	Present	Absent	Present (vestigial)	Present (vestigial)	Absent
	Number of digits (ant/post)	5/5	5/ 5	5 /5	4/ 5	4/5	4/3	5/4	4/4
Digestive apparatus	***Teeth***	Diphyodont Heterodont Bunodont (premolars, molars) *Dental Formula*: 2/2 1/1 2/2 3/3	Monophyodont Heterodont Lophodont Diastema *Dental Formula*: 1/1 0/0 0/0 3/3				Monophyodont Heterodont Lophodont Diastema *Dental Formula*: 1/1 0/0 1/1 3/3	Diphyodont Heterodont Two pair of upper incisors. Ever-growing incisors Diastema Lophodont *Dental Formula*: 2/1 0/0 3/2 3/3	Diphyodont Heterodont Bunodont (premolars, molars) *Dental Formula*: 3/3 1/1 4/4 3/3
	Ascending colon	Straight	Straight				Looped	Looped	Looped (spiroid colon)
	Gall bladder	Present	Present	Absent	Absent	Present	Present	Present	Present
	Cecal appendix	Present	Absent	Absent	Absent	Absent	Absent	Present	Absent
Female reproductive system	***Type of uterus***	Simple acorn	Simple bicorn	Simple bicorn bipartite	Simple bicorn	Simple bicorn	Simple bicorn	Double	Simple bicorn bipartite
	Mammary glands	2	10	10-12	12-16	8	2	8-10	10-14
Immune system and blood	***Tonsils***	Present	Absent	Absent	Absent	Absent	Present	Present	Present
	Neutrophil Lymphocyte % in peripheral blood (min-Max)	N 40-75% L 20-50%	N 7-37% L 63-75%	N 30% L 65%	N 7-37% L 63-75%	N 18-34% L 70-76%	N 28-44% L 39-72%	N 25-46% L 39-68%	N 28-47% L 39-62%

Table legend: General anatomical features of rodents (mouse, rat, hamster, gerbil, guinea pig), rabbit, and pig used in biomedical research compared to those in humans. Dental formulas of diphyodonts are those of permanent dentition. See text for additional data.

Table 3

Common name	**Scientific name**
Golden (Syrian) hamster	*Mesocricetus auratus*
Chinese (striped-back) hamster	*Cricetus griseus*
European hamster	*Cricetus cricetus*
Dzungarian (Siberian) hamster	*Phodopus sungorus*
South African hamster (white-tailed African rat)	*Mystromys albicaudatus*
Turkish hamster	*Mesocricetus brandti*
Armenian (gray) hamster	*Cricetulus migratorius*

Table legend: List of the species of hamsters currently used in biomedical research.