DELIVERABLE

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D2.1 Functional specifications - learning from the best - bird and fish lungs

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CONTENTS

1 EXECUTIVE SUMMARY

This document presents the deliverable D2.1 “Functional specifications - learning from the best – “bird lung and fish gills” of the EIC Pathfinder Open project BioMembrOS. It summarizes the key results achieved in Task 2.1 from project month M1 until M6. In this task, functional specifications of the BioMembrOS respiration device have been fully defined. Functional characteristics of respiration in birds and fish have been studied in detail based on extensive literature research in previously published research by the UJ partner. Based on these findings, it has been defined, which functional features shall be mimicked in the BioMembrOS workpackages WP3, 4, 5, 6 and 7 so as to develop a device with maximum performance and hemocompatibility that is suitable for an intracorporeal respiration device. In addition, performance criteria for the early laboratory demonstrator, the respiration membrane prototype (WP6) will be defined.

2 KEY WORD LIST

Air
Air capillaries
Air sacs
Atria
Avian lung
Basement membrane (base membrane)
Bird
Blood
Blood capillaries
Blood-gas barrier
Countercurrent exchange system
Crosscurrent exchange system
Diffusing capacity
Fish
Fish Gills
Gas exchanger
Gill filament
Gill arch
Gills
Harmonic mean thickness of the blood-gas barrier
Infundibula
Mammal
Morphometry
Morphometric diffusing capacity
Multicapillary serial arterialization system
Oxygen
Parabronchi
Pulmonary capillary blood volume
Respiratory surface area
Secondary lamella
Unidirectional airflow
Viscosity
Water
Water-blood barrier

3 LIST OF ACRONYMS

AC .... Air Capillaries
AL............. Avian Lung(s)
ARS .... Avian Respiratory System
AS .... Air Sac(s)
ASL........... Above Sea Level
BC .... Blood Capillaries
BGB........... Blood-Gas Barrier
BHG .... Bar-Headed Goose
CoCGES ..... CounterCurrent Gas Exchange System
CoCLGES ... CounterCurrent-Like Gas Exchange System
CrCGES...... CrossCurrent Gas Exchange System
CO_2........... Carbon dioxide
ET.............. Exchange Tissue
FG .... Fish Gills
GA............. Gill Arch
GF .... Gill filament
ML............. Mammalian Lung(s)
MCSAGES.. MultiCapillary Serial Arterialization Gas Exchange System
OD............. Oxygenation Device
O_2............. Oxygen
PL.............. Parabronchial Lumen
PCBV .... Pulmonary Capillary Blood Volume
PCO_2 .... Partial pressure of carbon dioxide
PO_2........... artial pressure of oxygen
RSA .... Respiratory Surface Area
RGV........... Ruppel's Griffon Vulture
SL .... Secondary Lamellae
WBB.......... Water-Blood Barrier
τht............ Harmonic mean thickness of the Blood-Gas Barrier

4 INTRODUCTION

Termed 'extraordinary creatures' and described as 'amazing' and 'most recognizable', birds are a considerably fascinating animal taxon. Historically, the so-called 'Darwin's finches' of the Galápagos Islands definitely instructed Charles Darwin on the understanding of the 'process of evolution by natural selection'. Currently, with recognition of the undesirable effects that global warming and climate change are imparting on the nature and the ecological distribution of plant and animal life, the biology of birds is becoming exceptionally instructive on the rate and the magnitude of the changes that are occurring. Properties such as variations in their migratory times, routes followed, distances covered and number of stopovers made during the flights are becoming important marks of environmental perturbations. For the reason that birds effortlessly and quickly desert harmful conditions, they (birds) are reliable 'bioindicator' or 'sentinel' species that indicate existence of injurious factors and changes in their habits, e.g. aspects such as contamination. In a certain habitat, the diversity of bird species and existence of large numbers reflect environmental well-being.

After the evolution of flight during the Late Jurassic period, ~150 million years ago, birds dispersed extensively. After occupying diverse ecological habitats, they underwent remarkable adaptive radiation, leading to great speciation that culminated in ~11,000 extant species. Among the contemporary species of birds, a body mass of ~20 kg appears to mark a decisive point at which capacity of powered flight is lost. Above that body mass, the flight muscles may not be capable of generating sufficient energy to lift the bird off the ground and keep it in the air. In the course of a free dive, the peregrine falcon (*Falco peregrinus*), the fastest known bird, attains a speed of 565 $km.hr^{-1}$. To relocate to favourable foraging places, avoid unsafe environmental conditions, escape from seasonal predators and acquire satisfactory reproduction sites, annually, ~1,800 species of birds undertake arduous migrations. From example, flying at an average speed of 146 $km.hr^{-1}$, a ~285 g body mass bar-tailed godwit (*Limosa lapponica*) is reported to have flown continuously across a distance of 28,000 km in only 8 days and the Arctic tern (*Sterna paradisea*), a bird of which the body mass was less than 125 g, flew over a distance of >80,000 km. Species of birds like the Ruppell's griffon vulture (RGV) (*Gyps rueppellii*), the bar-headed goose (BHG) (*Anser indicus*) and the Andean goose (*Chloephaga melanoptera*) that fly to and at extremely high altitudes have been termed as 'super birds'. A RGV vulture is reported to have hit an aeroplane at an altitude of 11.3 km

(37,073.49 feet) above sea level (ASL) and annually, the BHG fly over the Himalayan mountains (to winter out around the lakes of South Central Asia) between altitudes of between 4,000 and 8,000 m ASL. At those high elevations, the life-threatening environmental conditions include lack of O_2 (hypoxia), extremely low temperatures, very cold dry air and severe ultraviolet radiation. Regarding the remarkable energetic requirement for powered flight and the challenges posed in extracting O_2 from the hypoxic air of the high elevation, it is axiomatic that birds should have evolved an exceptionally efficient respiratory system.

From available documented accounts, the biology of the avian respiratory system (ARS) has been investigated for more-or-less five centuries. While some aspects have been worked out, others observations/findings have been controversial and others remain unresolved. Among the gas exchangers that have evolved in the air-breathing vertebrates, functionally, the ARS is the most efficient compared to any other vertebrate. The novelty of the ARS parallels the lifestyle that birds lead, especially that of powered flight. The structural and functional aspects of the ARS are outlined below.

5 DETAILED DESCRIPTION ON FUNCTIONALITIES

5.1 Structure and Function of Bird Lungs

Among the air-breathing vertebrates, the ARS, the lung-air sac system, is structurally the most complex. It is separated into lungs that are the site of gas exchange and air sacs (AS) (Fig. 1a) that ventilate the lung continuously and unidirectionally in a caudocranial direction, i.e., back-to-front. The AS connect to the lungs at sites called ostia (Fig. 1b, c). Avascular, the AS are not directly involved in gas exchange. Firmly attached to the vertebrae and the ribs, the avian lungs (AL) are practically rigid, i.e., inflexible. A three-tiered airway system that comprises an intrapulmonary primary bronchus, four sets of secondary bronchi and copious parabronchi (tertiary bronchi exist in the AL (Fig. 1b, c). A parabronchus consists of a lumen that is surrounded by a gas exchange tissue (ET) mantle Fig. 1d). The atria project outwards from the parabronchial lumen (PL) into the ET (Fig. 1d) where they form infundibula that in turn originate air capillaries (AC) (Fig. 1d).

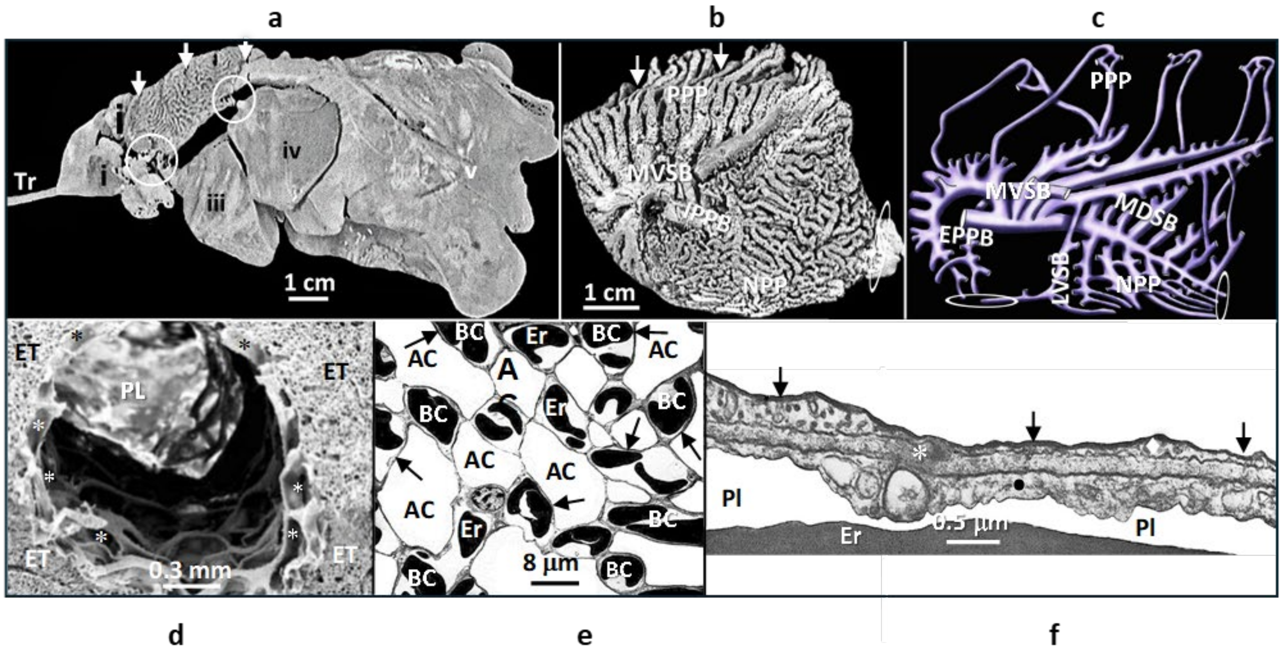


Figure 1: **a:** Lateral view of a latex rubber cast preparation (LRCP) of the respiratory system of the domestic fowl (DF) (*Gallus gallus* variant *domesticus*). i-iv, air sacs; circles (O), ostia; arrows (↓), costal sulci; Tr, trachea. **b:** Medial view of a LRCP of the lung of the DF showing the intricate airway system. PPP, paleopulmonic parabronchi; MVSB, medioventral secondary bronchi; IPPB, intrapulmonary primary bronchus; NPP, neopulmonic parabronchi; encircled area, ostium. **c**: Lung of the DF drawn as if transparent to show the complexity of the airway system. PPP, paleopulmonic parabronchi; NPP, neopulmonic parabronchi; MVSB, medioventral secondary bronchi; MDSB, mediodorsal secondary bronchi; EPPB, extrapulmonary primary bronchus; IPPB, intrapulmonary primary bronchus; encircled areas (O), ostia. The laterodorsal secondary bronchi are omitted to simplify the figure. **d**: Transverse view of a parabronchus of the lung of the DF. PL, parabronchial lumen; ET, exchange tissue; asteriscs (∗), atria. **e**: Exchange tissue (ET) of the lung of the house sparrow (*Passer domesticus*) showing air capillaries (AC) and blood capillaries (BC) that closely entwine. Arrow (↓), blood-gas barrier (BGB); Er, erythrocytes. **f**: The BGB of the lung of the DF. Arrows, surface lining (surfactant); diamonds (♦), epithelial cell; asterisks (∗), basement membrane; dots (●), endothelial cell; Er erythrocyte; Pl, plasma layer.

The blood capillaries (BC) and the AC entwine intimately. They form the terminal respiratory units of the AL (Fig. 1e). A thin blood-gas (tissue) barrier that comprises a surfactant lining, an epithelial cell, a common basement membrane and an endothelial cell (Fig. 1f) separates the BCs and the ACs.

The airway (bronchial)- and the vascular systems of the AL respectively deliver air and supply blood to the lung (via the pulmonary artery) and return it to the heart by the pulmonary vein. In the ET, blood is presented to air across the blood-gas barrier (BGB), where O_2 is taken up and CO_2 eliminated. In the ET of the parabronchi of the AL, a crosscurrent gas exchange system CrCGES)-, a countercurrent like system (CoCGES) and a multicapillary serial arterialization system (MCSAS) coexist. They derive from the organization of the airway- and the vascular systems. The exceptional respiratory efficiency of the ARS stems from a complex synergy of morphological properties and physiological processes by which O_2 uptake is optimized to support the high metabolic states and capacities that characterize birds. Given that among the extant volant animal taxa, namely insects, birds and bats, possess structurally different respiratory systems, respectively the tracheal system, the parabronchial lung and the bronchioalveolar lung, the ARS is not a prerequisite for attainment of powered flight: it was an adaptive evolutionary solution to realization of an exceptionally efficient mode of locomotion.

5.2 Morphometrics of Bird Lungs

The volume of the AL, the respiratory surface area (RSA), i.e., the surface area of the BGB, the volume of the pulmonary capillary blood (PCBV) and the harmonic mean thickness of the BGB (τht) are the most important morphometric parameters that structurally explain the gas exchange efficiency of the AL. For birds, the volume of the lung (VL) comprises as much as 34% of the volume of the body. For animals of equivalent body mass, compared with that of a nonflying mammal of equivalent body mass, the volume of the AL is ~27% smaller. The value (VL) correlates strongly (r = 0.9970) and scales positively (b = 1.5467) with body mass (Fig. 2a). With respective values of 42.8- and 42.9 $cm^3.kg^{-1}$, among the species of birds that have been investigated, the Andean goose (*Chloephaga melanoptera*) and the volet-eared hummingbird (*Colibri coruscans*) have the highest mass-specific VL. From the extreme subdivision of the ET of the AL, the surface density of the RSA, i.e., surface area of the BGB per unit volume of the ET, correlates strongly (0.7679) and scales negatively (-0.1031) with body mass (Fig. 2b). Although birds have relatively smaller lungs, the RSA of their lungs is ~15% greater than that of a nonflying mammal of equivalent body mass. The unexpected outcome comes from the rigidity (inflexibility) of the AL that leads to extreme subdivision, i.e., compartmentalization, of the ET into minuscular terminal respiratory units (the AC) that are ~8-20 μm in diameter: the intense subdivision of the ET generates large RSA in the small AL. Strong positive correlation (r = 0.9952) and scaling (b = 0.8674) exists between the RSA of the AL and body mass (Fig. 2c). Among the species of birds that have been investigated, respectively, the mass-specific RSA of the lungs of the Andean goose and the violet-eared hummingbird, i.e., 96.5- and 87.1 $cm^2.g^{-1}$, are the highest. The τ_{ht} of a bird's lung is ~2.5 and ~56 to 67% times smaller than that of a nonvolant mammal equivalent body mass (Fig. 2d). With τht values of respectively 0.099- and 0.090 µm, among birds, the violet-eared hummingbird and the African rock martin (*Hirundo fuligula*) have the thinnest BGBs. The lungs of the ostrich (*Struthio camelus*), the Humboldt penguin *(Spheniscus humboldti)* and the Chilean tinamou *(Notoprocta perdicaria)*, with respective τhts of 0.56-, 0.53- and 0.47 µm, have among the AL that have been studied the thickest BGBs. In birds, weak correlation (r = 0.4512) and low scaling (b = 0.0687) exist between the thickness of the BGB ((τ_{ht})) and body mass. In the AL, the volume of blood comprises as much as 36% of that of the organ: 58-80% of it located in the BC. The PCBV correlates (r = 0.9899) and scales (b = 0.9594) strongly with body mass (Fig. 2e). For birds, the total pulmonary morphometric diffusing capacity of O_2 or its conductance for O_2, a comprehensive parameter that specifies the conductance of O_2 by a gas exchanger, correlates- (r = 0.9863) and scales (b = 0.9198) strongly with body mass (Fig. 2f).

A summary of pulmonary morphometric parameters of bird lungs for different birds (birds of different sizes and lung sizes) is given in Table 1.

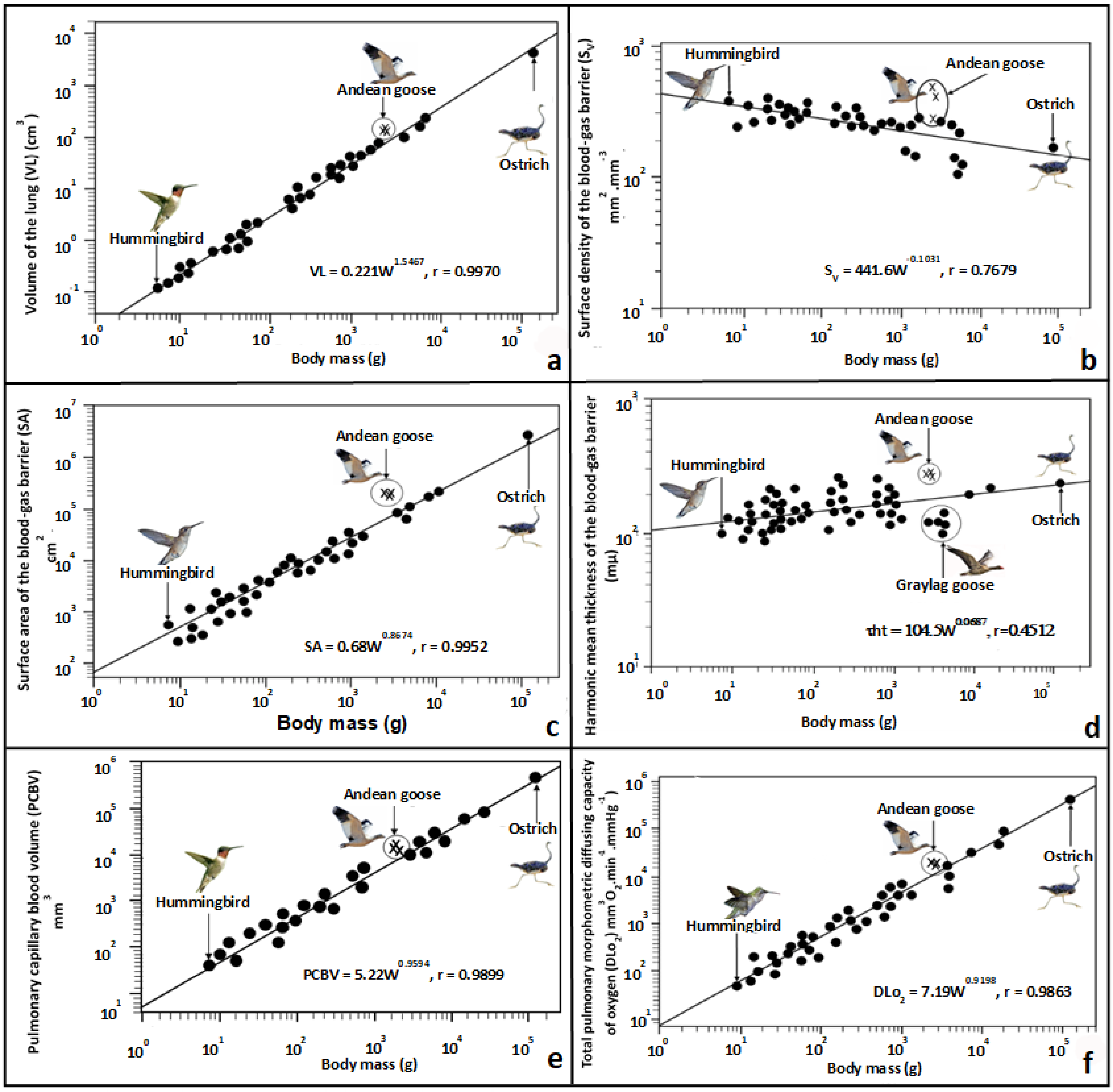


Figure 2: Allometric relationships of pulmonary morphometric parameters in birds. **a:** Relationship between the VL and body: strong positive correlation exists between the parameters. **b:** Relationship between the surface density of the blood-gas barrier (BGB) and body mass: strong negative correlation exists between the parameters. **c:** Relationship between the respiratory surface area and body mass: strong positive correlation exists between the parameters. **d:** Relationship between the harmonic mean thickness of the BGB and body mass: weak positive correlation exists between the parameters. **e:** Relationship between the pulmonary capillary blood volume and body mass: strong and positive correlation exists between the parameters. **f:** Relationship between the total pulmonary diffusing capacity and body mass: strong and positive correlation exists between the parameters.

Table 1: Comparison of the mean values of the pulmonary morphometric parameters of the lungs of some species of birds. Harmonic mean thickness of the blood-gas (tissue) barrier (τht), volume of the lung per unit body mass ($VL.BM^{-1}$), pulmonary capillary blood volume per unit body mass ($PCBV.BM^{-1}$), pulmonary capillary blood volume per unit surface area of the blood-gas (tissue) barrier ($PCBV.S_{(BGB)}{}^{-1}$), surface area of the blood-gas barrier (BGB) per unit body mass ($S_{(BGB)}.BM^{-1}$), surface area of the BGB per unit volume of the lung parenchyma (exchange tissue) ($S_{(BGB)}.V_{(LP)}{}^{-1}$)), morphometric diffusing capacity of the BGB per unit body mass ($Dto_2.kg^{-1}$) and the total pulmonary morphometric diffusing capacity of the lung per unit body mass ($DLo_2.kg^{-1}$).

Common English name/ Latin name	**τht (μm)**	**$VL.BM^{-1}$ ($cm^3.kg^{-1}$)**	**$PCBV.BM^{-1}$ $cm^3.kg^{-1}$**	**$PCBV.SBGB^{-1}$ ($cm^3.m^{-2}$)**	**$S_{(BGB)}.BM^{-1}$ ($cm^2.g^{-1}$)**	**$S_{(BGB)}.V_{(LP)}{}^{-1}$ ($mm^2.mm^{-3}$)**	**$DtO_2.kg^{-1}$ ($mlO_2.sec^{-1}.mbar^{-1}.kg^{-1}$)**	**$DLO_2.kg^{-1}$ ($mlO_2.sec^{-1}.mbar^{-1}.kg^{-1}$)**
Andean goose *Chloephaga melanoptera*	0.222	42.8	7.39	0.78	96.2	364	1.79	0.119
Domestic fowl *Gallus domesticus*	0.318	12.6	1.63	1.6	8.7	172	0.20	0.015
Ostrich *Struthio camelus*	0.560	38.1	5.46	2.08	30.1	98.3	0.13	0.065
Graylag goose *Anser anser*	0.118	30	3.25	1.4	23.1	253	0.88	0.045
Spectacled guillemot[e] *Larus argentatus*	0.153	27.8	4.34	1.5	22.1	236	0.55	0.034
Rock dove *Columba livia*	0.061	34.3	5.01	1.3	39.8	254	1.02	0.093
Budgerigar *Mellopsitacus undulatus*	0.117	28.3	4.39	1.1	42.6	317	2.90	0.055
Violet-eared hummingbird *Colibri coruscans*	0.099	42.9	7.00	1.0	87.1	389	3.56	-
Emu *Dromaius novaehollandiae*	0.232	36.7	5.55	1.7	5.4	82	0.100	0.013
Humboldt penguin *Spheniscus humboldti*	0.530	30.4	79.59	4.4	18.1	116	0.014	0.051
African rock martin *Hirundo fuligula*	0.090	24.1	5.46	0.7	86.5	353	4.015	4.015
House sparrow *Passer domesticus*	0.096	29.8	6.31	0.9	63.0	389	2.292	2.902
Muscovy duck[m] (Domestic) *Cairina moschata*	0.199	30.0	4.31	1.5	30.0	200	0.62	0.06

5.3 Functional Aspects of Avian Lungs

For the AL, gas exchange occurs in the ET, most of which is located in the parabronchi (Fig. 1d). As air flows through the PL, it travels outwards, i.e., centrifugally, into the ET. Concurrently, deoxygenated (venous) blood flows inwards, i.e., centripetally, from the periphery into the ET (Fig. 3a, b). The perpendicular (orthogonal) disposition between the directions of air flow (in the PL) and that of blood (venous) into the ET forms the cross-current gas exchange system. Because in the ET of the parabronchi of the AL venous blood flows 'inwards', i.e., from the periphery inwards, and air travels 'outwards' from the PL into the ET (Fig. 3a, b), a COCLGES reportedly exists in the AL. In a parabronchus, venous blood is delivered about the same time to all parts of the ET by the intraparabronchial arteries (Fig. 3a, b). In the BC, blood equilibrates with air in the ET (specifically in the AC) of changing composition of respiratory gases (O_2 and CO_2). At the entrance of a parabronchus, venous blood is exposed to air with high PO_2 and low PCO_2 while at the outlet, gas tensions are reversed, i.e., PO_2 is lower and PCO_2 greater: the arrangement constitutes a multicapillary serial arterialization gas exchange system (MCSAGES). Oxygen and CO_2 are exchanged across the greatly many points in the ET where the ACs and the BCs contact (Fig. 3a, b). From the

MCSAGES, the quantity of O_2 contained in the oxygenated (arterial) blood returning to the heart (via the pulmonary veins) derives by an additive process where minuscular gas exchange events occur at the many points where the ACs and the BCs interface. Importantly, by prolonging the time and area of exposure of blood to air, the MCSAGES enhances gas exchange efficiency.

a b

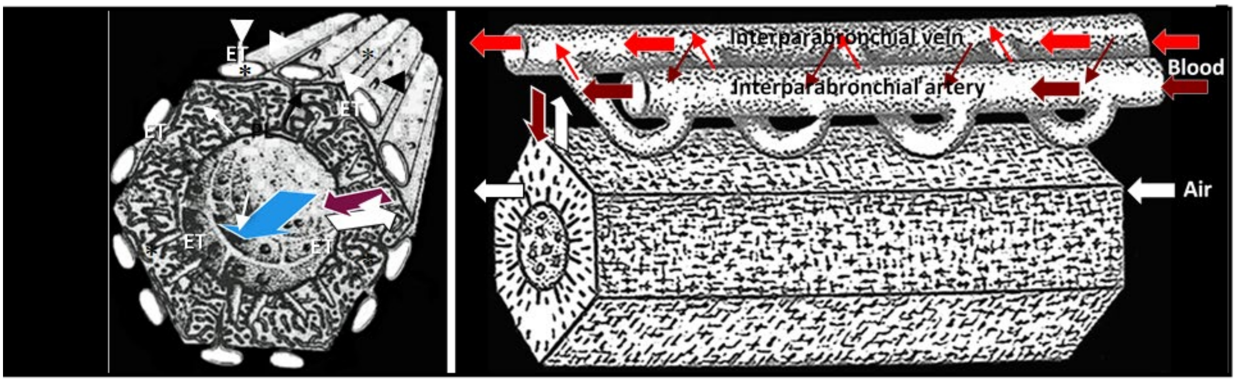


Figure 3a, b: Gas exchange functional designs the avian lung. Schematic drawings of a parabronchus showing the parabronchial lumen (PL) that is surrounded by exchange tissue (ET). The crosscurrent gas exchange system comprises the relationship between the directions of the air flowing in the parabronchial lumen (blue arrows) and the venous (deoxygenated blood) flowing towards the PL. The countercurrent gas exchange system comprises the relationship between air flowing outwards into the exchange tissue (white arrow) and that of venous blood from the periphery of the ET (brown arrows). The multicapillary serial arterialization system comprises the infinitely many gas exchange arrangements between air- and blood capillaries in the ET to a parabronchus. Thin arrows (↓), atria; asterisks (∗), interparabronchial arteries; arrowheads, intraparabronchial arteries.

5.4 Structure and Function of Fish Gills

Fish gills (FG) develop as evaginated outgrowths of the pharyngeal region of the body. Water-breathing organs, the gills are delicate structures that are permeable to the respiratory gases (O_2 and CO_2). Depending on their position and structure, the vertebrate gills are classified as internal- and external types. The former are simple structures that dangle freely in the surrounding water while the later, that are structurally more complicated, are located in the pharyngeal cavity where depending on species are covered by a fixed mesenchymal tissue mass (e.g., in the elasmobranchs) or a movable flap termed operculum (e.g., in the teleost fish). For the later, the gills comprise four pairs of gill arches (GA) that are contained in the branchial cavity where they are protected by an operculum. The GA comprise hundreds of gill filaments that generate thousands of secondary lamella (SL) (Fig 4a-d). In the FG, gas exchange occurs across the semicircular (flap-like) structures, the SL that are bilaterally arranged along the lengths of the gill filaments (GF) (Fig. 4 a-d). Structurally, the water-blood barrier (WBB) of the FG is a tripartite structure. It comprises an epithelial cell, a basement membrane (= base membrane,: a thin, pliable sheet-like type of extracellular matrix that provides cell and tissue support) or an interstitial space and an endothelial cell (Fig. 4g, h).

Displaying a stratified, i.e., hierarchical or brachiate, morphology, the FG present a fractal morphology. The design generates vast RSA and large capillary blood volume in a confined space, i.e., the fixed brachial cavity.

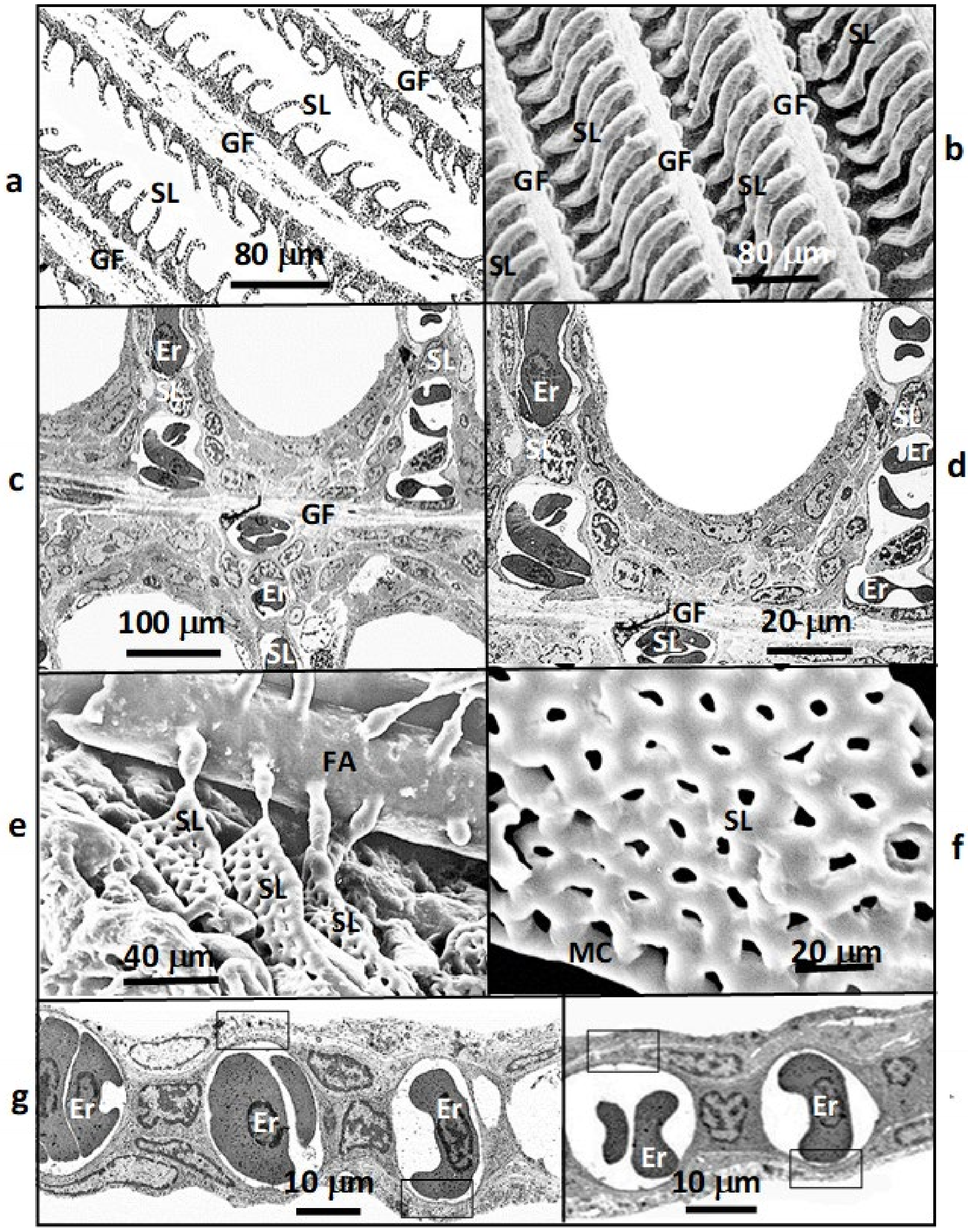


Figure 4a-d: Gills of a tilapiine fish (*Orechromis alcalicus*) showing gill filaments (GF) and secondary lamellae (SL). Er, erythrocyte. The hierarchical organization of the gills where eight gill arvhes give rise to hundreds of gills filaments and thousands of secondary lamellae give rise to large respiratory surface area. **e, f**: Secondary lamellae (SL) that are well-vascularised. FA, filamental artery; MC, marginal channel. **g, h**: The water-blood barrier (boxed areas) of the fish gills. Er, erythrocytes.

5.5 Morphometrics of Fish Gills

Compres with the mammalian- and avian lungs, the morphometric details on the FG are less available. Table 2 gives an overview of such data of gills of common fish species.

Table 2: Morphometrics of fish gills including thickness information about the water-blood barrier, respiratory surface area and diffusion capacity of the water-blood barrier.

Common English name/Latin name	Thickness of the water-blood barrier (μm)	Respiratory surface area ($cm^2.g^{-1}$)	Diffusing capacity of the water-blood barrier ($mlO_2.min^{-1}.mmHg^{-1}.kg^{-1}$)
Tench *(Tinca tinca)*	2.473	2.275	0.1493
Thornback ray *(Raia clavate)*	6.0	1.235	-
Small-spotted catshark *(Scyliorhinus canicula)*	11.3	2.1	-
Spiny dogfish *(Squalus acanthias)*	10.1	3.70	10.14
Skipjack tuna *(Katsuwonus pelamis)*	0.598	13.5	0.59
Bluefin tuna *(Thunnus thynnus)*	-	8.85	-
Common dragonet *(Callionymus lyra)*	-	2.06	-
Coelacanth *(Latimeria chalumnae)*	5-6	0.189	-
Oyster toad *(Opsanus tau)*	5	1.92	-
Blackfin icefish *(Chaenocephalus aceratus)*	-	1.08	-
Black southern cod *(Notothenia tessellate)*	-	5.18	-
Brown bullhead *(Ameiurus - Ictalurus - nebulosus)*	-	1.17	-
European eel *(Anguilla anguilla*	-	9.9	-
Goldfish *(Carassius auratus)*	-	1.16	-
Common carp *(Cyprinus carpio)*	-	1.39	-
Brown trout *(Salmo trutta)*	-	3.39	-
Rainbow trout *(Salmo gairdneri)*	-	3.59	6.37
Tench *(Tinca tinca)*	-	1.83	2.5
Atlantic horse mackerel *(Trachurus trachurus)*	2.221	-	-
Magadi tilapia *(Oreochromis alcalicus graham)*	0.83		0.99
Nile tilapia *(Oreochromis niloticus)*	1.25		0.76

6 COMPARISON OF STRUCTURE AND FUNCTION OF FISH GILLS AND AVIAN AND MAMMALIAN LUNGS

6.1 Fish Gills

Air and water are the only two naturally available respirable fluid media. The physicochemical differences between them have greatly determined the evolution of the respiratory processes and mechanisms. The remarkable differences should have prevented direct evolution, i.e., conversion, of gills to lungs: a transitory stage, where air- and water-breathing organs coexisted as gas exchangers, was therefore obligatory. Because of the relatively lower concentration of O_2 in water and its higher viscosity that makes it energetically more costly to breath, the highly efficacious countercurrent gas exchange system (CoCGES), where in the gills, water and blood flow in opposite directions, was necessary (Fig. 5). The adaptation offset limiting structural parameters such as relatively lower RSA, i.e., the surface area of the WBB and the WBB is thicker.

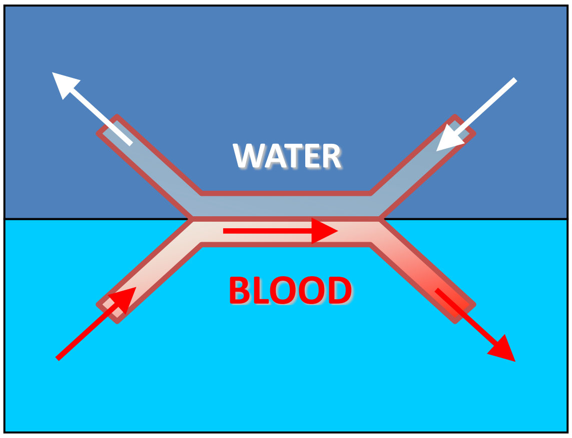


Figure 5: Representation of counter-current flow as the functional principle of fish gills.

The morphology of the mammalian lung (ML) has invited terms such as 'brionchioalveolar lung' and 'respiratory tree'. Respectively, the airways branch regularly (Fig. 6a) to terminate in alveoli that form a canopy-like shape (Fig. 6b-f). Although mammals and birds are the only extant endothermic vertebraes, their lungs differ structurally and functionally: a) while the AL is inflexible and ventilated continuously and unidirectionally (by the AS), the mammalian one is compliant and is ventilated tidally, i.e., in-and-out; b) the arrangement of the structural components, namely the airways and the blood vessels, of the AL generate CrCGES-, CoCLGES and MCSAGES that do not exist in the mammalian one where a 'uniform pool design exists; c) with relatively larger respiratory surfaces, large PCBV and thinner BGB, morphometrically, compared with the ML, the total pulmonary morphometric diffusing capacity of the AL for O_2 is greater than the mammalian one. For example, for the 4.5 L lung volume of a 75 kg body mass human being, the RSA is 142 m^2 and the τht is 0.65

μm while for a 50 kg body mass ostrich, the respective values are 183 m^2 and 0.56 μm. Compared to mammals, structurally and functionally, birds have a superior respiratory system.

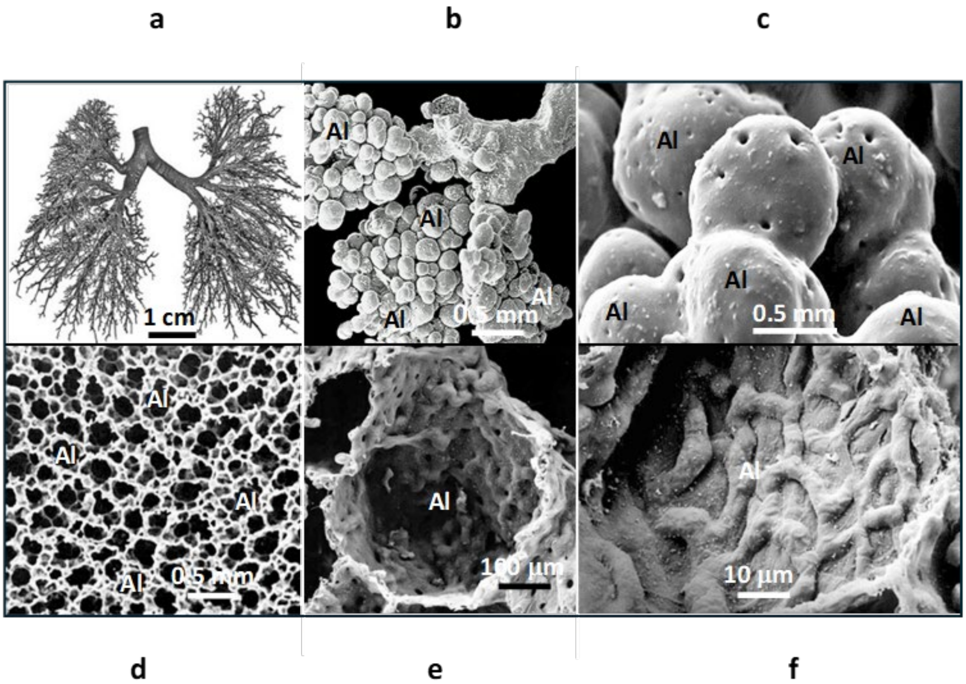


Figure 6: Human lung. **a**: Latex rubber cast preparatio of the human lung showing bifurcation of the airways. **b**: Acinus giving rise to alveoli (Al). c: alveoli (Al). d-f: Parenchyma (d) and alveoli (Al) (e, f).

6.2 Bird Lungs

Although birds have relatively small lungs (Fig. 7a), because of the rigidity of their lungs and the ensuing extreme subdivision of the ET, compared with nonflying mammals bird lungs have larger RSA. I comparison with bats and nonflying mammals, bird lungs have a relatively thinnner blood gas barrier (Fig. 7b).

In gas exchangers, the structure of the WBB (in water-breathing animals) and the BGB (in water-breathing animals) is tripartite in nature (Fig. 8): they comprise an epithelial cell, a basement membrane and an endothelial cell (Fig. 8). It shows a degree of conservation of a structural design to meet specific function – gas exchange by diffusion.

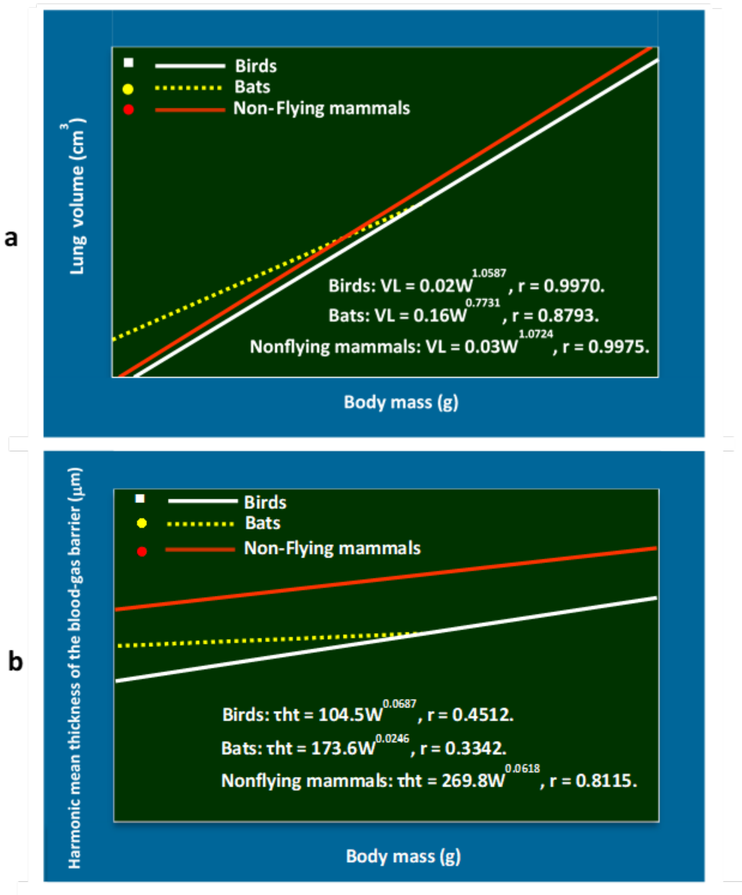


Figure 7a, b: Allometric relationhips between lung volume and thickness of the blood-gas barrier in birds, bats and nonflying mammals. Birds have relatively smaller lung and thinner blood-gas barriers.

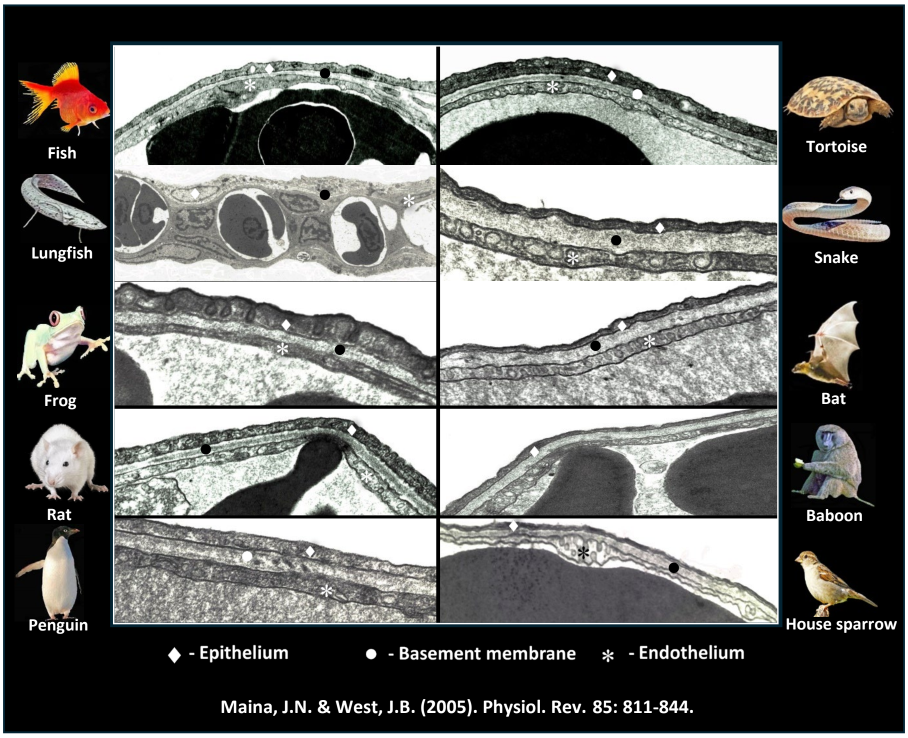
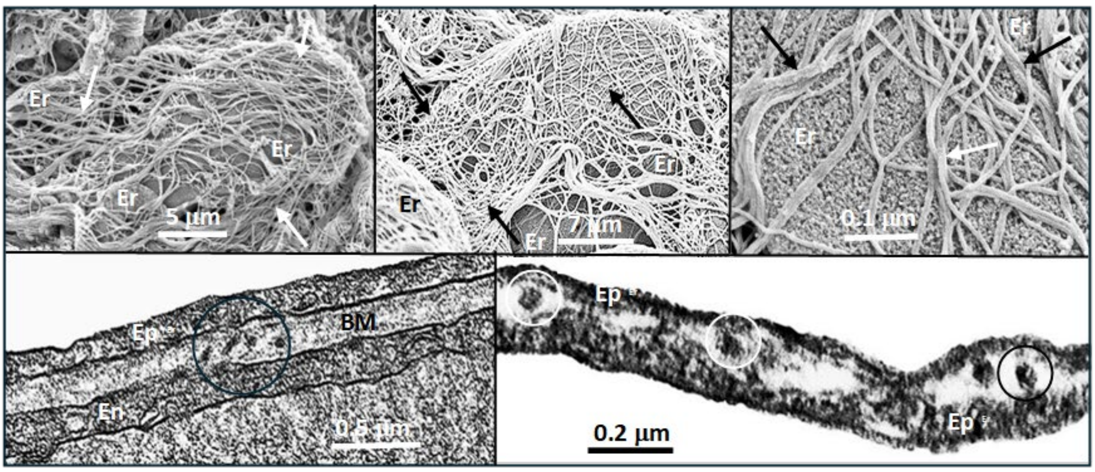


Figure 8: Evolutionary conservation of the tripartite structure of the tissue barriers of the vertebrate gas exchangers. e

6.3 The Functional Role of Collagen Fibers

Collagen fibers provide strength and support to the body. This is particularly important for the BGB of the gas exchangers. Paradoxically, the WBB and the BGB have to be thin to optimize the flux of respiratory gases (O_2 and CO_2) by diffusion and to tolerate pressures and tensions that come from ventilatory movements. Furthermore, at the BC level, the tissue barriers have to tolerate pressures that originate from the beating heart. Compared with mammals, birds in general have higher systemic blood pressures. In the lungs of mammals and birds, collagen type-IV has been associated with the strength of the BGB. It, however,

a b c



d e

Figure 9: a-c: Macerated blood vessels of the lung of the domestic fowl (*Gallus gallus* variant *domesticus*) showing erythrocytes (Er) flowing through blood bessels and collagen fibers (arrows) in their walls. **d, e**: Blood-gas barrier (d) and epithelial-epithelial connection (e) of the lung of the domestic fowl showing collagen fibers (encircled areas. Ep, epithelial cell; BM, basement membrane; En, endothelial cell.

remains to be determined how the fibers are arranged in the basement membrane.

6.4 Provenance of the structure and function of fish gills and the avian lung and design of an oxygenation device

Evolutionary, the fish gills are specialised for gas exchange with water. The CoCGES is the most important important aspect that can be borrowed and applied to the design of the envisaged extracorporeal oxygenation device (OD) in the BiomembrOs project. For the AL, large RSA, thin BGB and large PCBV, parameters that originate high pulmonary morphometric diffusing capacity for O_2 should be replicated in the design of the OD. Ranking of the functional efficiencies of the evolved gas exchangers shows that the ML is modest. It does not offer any functional or structural specialization worthy emulating in the design of the considered OD.

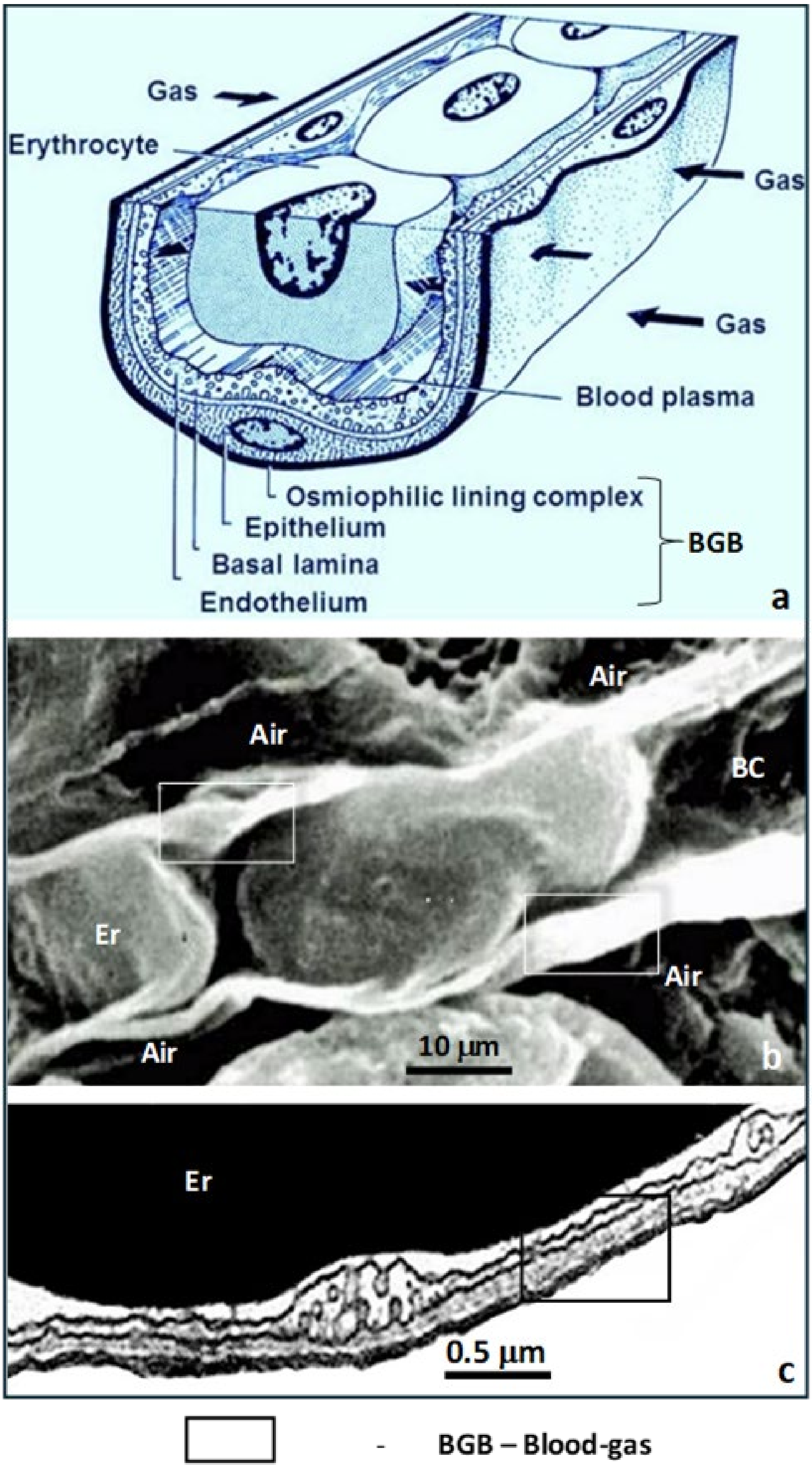


Figure 10: a: A stereogram of a pulmonary blood capillary showing the structural components that comprise the blood-gas barrier across which oxygen diffuses. **b**. A scanning electron micrograph showing erythrocytes (er) flowing through a blood capillary (BC). A blood-gas barrier (boxed areas) separates blood from air. c: A transmision electron micrograph showing the blood-gas barier (boxed area). Er, erythrocyte.

7 BIOMIMETIC SPECIFICATIONS FOR THE CONSTRUCTION OF THE OXYGENATION DEVICE

From the functional performance of the AL and FG, the following conclusions can be drawn:

1. For effective gas exchange by diffusion and to ensure structural integrity, the membrane partitioning of the device should be thin and strong.

2. To enhance gas exchange efficiency, a CoCGES should be inbuilt in the device.

3. The surface area across which the gas exchange fluid media (blood and water/air) are exposed to each other and their volumes should be optimized towards avian systems.

8 LIST OF FIGURES

9 LIST OF TABLES

10 FURTHER READING

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