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1 **The pig as a medical model for acquired respiratory diseases and dysfunction: an immunological**  
2 **perspective**

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6

7 **Abstract**

8 By definition no model is perfect, and this also holds for biology and health sciences. In medicine,  
9 murine models are, and will be indispensable for long, thanks to their reasonable cost and huge  
10 choice of transgenic strains and molecular tools. On the other side, non-human primates remain the  
11 best animal models although their use is limited because of financial and obvious ethical reasons. In  
12 the field of respiratory diseases, specific clinical models such as sheep and cotton rat for  
13 bronchiolitis, or ferret and Syrian hamster for influenza and Covid-19, have been successfully  
14 developed, however, in these species, the toolbox for biological analysis remains scarce. In this view  
15 the porcine medical model is appearing as the third, intermediate, choice, between murine and  
16 primate. Herein we would like to present the pros and cons of pig as a model for acquired respiratory  
17 conditions, through an immunological point of view. Indeed, important progresses have been made  
18 in pig immunology during the last decade that allowed the precise description of immune molecules  
19 and cell phenotypes and functions. These progresses might allow the use of pig as clinical model of  
20 human respiratory diseases but also as a species of interest to perform basic research explorations.  
21

22 **Generalities**

23 In its ‘Global Impact of Respiratory Disease’, the World Health Organization (WHO) identifies  
24 ‘the big five’ respiratory diseases as chronic obstructive pulmonary disease (COPD), asthma, acute  
25 lower respiratory tract infections, tuberculosis and lung cancer. Moreover, according to Eurostat  
26 report, diseases of the respiratory system accounted for 7.5 % of all deaths in the European Union in  
27 2016 (Eurostat, 2020), and these statistics do not take into account the current SARS-CoV-2  
28 pandemic which will probably become the infectious disease associated to the highest number of  
29 fatalities in 2020. In the pathophysiology of all these diseases, the immune system has definitely a  
30 central role and we need to better understand how it operates in order to prevent and treat the  
31 respiratory diseases.

32 Current Food and Drug Administration (FDA) guidelines require testing of new  
33 pharmaceutical agents in both small and large animal models when proving a therapeutic concept  
34 (FDA, 2015). We advocate herein to consider pig as a model of choice when investigating the  
35 immunological side of respiratory diseases.

36 The *Suidae* family (swine, wild boar, red river hog, and warthog to cite the best known) is  
37 evolutionary more distant from the *Hominidae* family (including human being and all the great apes)  
38 than the *Muridae* family (mouse, rat, hamster and naked mole rat). Indeed, men and mice belong to  
39 the same *Euarchontoglires* superorder whereas pigs belong to the *Laurasiatheria* superorder. Despite  
40 this, and probably as a consequence of the faster genetic evolutionary rate of mouse, the pig genome  
41 has remained more similar to the human one both in terms of DNA sequences than in term of genes’  
42 synteny (Humphray et al., 2007; Wernersson et al., 2005). Because of this genetic proximity and for  
43 other reasons listed below, the pig has been largely used as a biomedical model and notably as a  
44 model for the study of human infectious diseases and for vaccine development (Gerdtts et al., 2015;  
45 Käser et al., 2018; Lunney, 2007; Meurens et al., 2012). In this review we focused especially on the  
46 pig as a model to study acquired respiratory diseases except cancer, at the light of the accumulating  
47 knowledge concerning the swine respiratory immune system.

48

## 49 **Porcine Respiratory System Structure**

50 The size and the weight of the pig is age-, sex- and breed-dependent. Some minipig breeds  
51 like the Yucatan or the Göttingen present adult pigs with size and weight similar to human adults  
52 making the breeds attractive in biomedical research (Meurens et al., 2012; Swindle et al., 2012).  
53 Overall, the porcine anatomy and physiology are quite similar to human anatomy and physiology,  
54 both species are all-eating for instance (Käser et al., 2018; Meurens et al., 2012; Swindle et al., 2012).  
55 Moreover, pigs are widely available with usually manageable size allowing for smooth handling and  
56 easy experimental interventions.

57 Regarding specifically the porcine respiratory tract, the pig has been extensively  
58 characterized and compared with the human one (Judge et al., 2014; Krejci et al., 2013) as well as in  
59 exhaustive reviews that were assessing its potential as a model for cystic fibrosis (Rogers et al., 2008)  
60 and asthma (Kirschvink and Reinhold, 2008). The respiratory tract can be divided into the upper and  
61 lower respiratory tracts. The upper respiratory tract is including the nasal cavities, the sinuses, the  
62 nasopharynx, the larynx and the trachea while the lower respiratory tract includes overall the lung  
63 with the bronchi, the bronchioles, the terminal and respiratory bronchioles, and alveoli. Air enters  
64 the porcine respiratory tract through round nostrils and a pair of nasal cavities situated in the snout  
65 (*rostrum*). In the nasal cavities, the epithelium is typically pseudostratified with ciliated columnar  
66 cells. The epithelium contains loose lymphocytes, lympho-reticular tissue aggregates and tubo-  
67 alveolar glands. Regarding submucosal glands in nasal turbinates and trachea, some differences have  
68 been shown between pigs and humans using the porcine cystic fibrosis model (Cho et al., 2011).  
69 Similarly, to humans, pigs have ethmoid and maxillary sinuses at birth and develop frontal and  
70 sphenoid sinuses (Sisson et al., 1975). Then, after its circulation in the nasal cavities, the air moves  
71 through the nasopharyngeal tube into the pharynx with the possibility to gain access to the  
72 esophagus. The respiratory part of the pharynx, called nasopharynx, also presents a pseudostratified  
73 ciliated columnar epithelium with goblet cells. In the upper respiratory tract, its nasal-associated  
74 lymphoid tissue (NALT) resembles the human's Waldeyer ring and pigs, like humans, possess several  
75 tonsils (*veli palatine*, *pharyngea*, *tubaria*, *paraepiglottica* and *lingualis*) (Horter et al., 2003; Liebler-  
76 Tenorio and Pabst, 2006; Swindle et al., 2012). This lymphoid tissue is comprised of the *Lamina*  
77 *propria mucosae* as well as fine glandules. Then, the larynx links the nasopharynx and the lower  
78 respiratory tract, including epiglottis and vocal cords. In the larynx the mucosa showed again a  
79 pseudostratified columnar epithelium with isolated goblet cells. In the submucosa of epiglottis, *plicae*  
80 *aryepiglotticae* and *vestibulum larynges*, an accumulation of lymphoid tissue is observed. The trachea  
81 consists of 32-36 C-shaped rings of hyaline cartilage with strong fibro-elastic membranes observed  
82 between the rings. The trachea shows a ciliated pseudostratified columnar epithelium and isolated  
83 goblet cells. Below, in the mucosa, small islets of lympho-reticular tissue and combined tubo-alveolar  
84 glands are observed. Regarding the gross anatomy of the porcine lung, two lobes on the left sides  
85 and four on the right have been described (Rogers et al., 2008; Swindle et al., 2012). On the left side,  
86 the lobes are designated as left cranial and caudal and on the right as right cranial, right middle, right  
87 caudal and right accessory. Interestingly, the right cranial lobe is directly linked to the trachea.  
88 Looking at subgross anatomy, pig like human lung, and in contrast to murine lung shows extensive  
89 intralobular and interlobular connective tissue. This tissue joins the bronchi and the main blood  
90 vessels to the pleural surface (Tyler, 1983). However, the interlobular collagenous network is  
91 incomplete in humans whereas in the pig the interlobular septa are "complete" blocking the  
92 collateral ventilation (Rogers et al., 2008; Woolcock and Macklem, 1971). The porcine pleura like its  
93 human counterpart is relatively thick and collagenous and has a vascular supply originating from the  
94 bronchial arteries (McLaughlin et al., 1961; Tyler, 1983). Regarding the lymph nodes (LN) in the  
95 thoracic cavity, they are concentrated into four lymphoid centres, two parietal (*thoracicum dorsal*

96 and *ventral*) and two visceral (*mediastional* and *bronchale*). Moreover, there are the LN adjacent to  
97 the bronchi (*tracheobronchales dextri, sinistri* and *medii*). While the vascular circulation of the pig  
98 follows a common pattern of organization and development with human vascular circulation there is  
99 an inverted structure of swine LN compared to their human and murine counterparts. Indeed, in  
100 most of the mammals, including mouse and man, afferent lymph percolates in a centripetal  
101 manner from the periphery to the center (hilum) of the node. In swine, the afferent lymph diffuses  
102 from the center to the periphery in a centrifugal manner (Mcfarlin et al., 1973). In addition, in pig,  
103 lymphocytes exit the LN through the high-endothelial venules whereas in mouse and man they exit  
104 through the efferent lymphatics (Sasaki et al., 1994). The functional implications of these oddities  
105 have not been explored yet. Overall, even if similar to human airways, the porcine airways show  
106 small differences (Haworth and Hislop, 1981; McLaughlin et al., 1961; Rendas et al., 1978): i) the  
107 cartilage around porcine airways is more developed than in humans; ii) a lower number of bronchi  
108 generations, after the last cartilage plate, has been reported in pigs compared to what is reported in  
109 humans; and iii) longer terminal bronchioles and overall less-defined respiratory bronchioles are  
110 described. At the microscopic level, porcine lungs show similar cell lineages to human lungs (Haworth  
111 and Hislop, 1981; Jones et al., 1975; Mills et al., 1986; Rogers et al., 2008; Winkler and Cheville,  
112 1984).

113

#### 114 **General systemic immunology**

115 Before addressing specifically the porcine lung immunology, a brief overview of the systemic  
116 porcine immune system is needed. Comparably to the whole genome comparisons, the immunome  
117 analysis demonstrated a greater similarity between human and pig than between human and mouse.  
118 However, a peculiarity of swine immune system that can be highlighted is the expansion of the type I  
119 IFN gene families, especially the IFN $\delta$  and the IFN $\omega$  (Dawson et al., 2013). IFN $\delta$  clearly distinguishes  
120 pig from human and mouse since pig has 11 functional IFN $\delta$  genes and mouse and man have none.  
121 IFN $\delta$  bind to the same type 1 receptor as IFN $\alpha$ , it has high antiviral and anti-proliferative activities on  
122 porcine cells, but not on human cells (Lefèvre et al., 1998). Conversely IFN $\omega$  separates mouse from  
123 the two other species since mouse has no functional IFN $\omega$  gene, man 1, and pig 7. IFN $\omega$  presented  
124 highly cross-species antiviral (but little anti-proliferative) activity (Jennings and Sang, 2019; Shields et  
125 al., 2019). A recent review summarized the different porcine cytokines, chemokines and growth  
126 factors, and described the tools available to study them (Dawson et al., 2020).

127 Looking more precisely at the different immune cell types, three relatively recent reviews  
128 have been published on the porcine innate immune response (Mair et al., 2014), mononuclear  
129 phagocytes (Fairbairn et al., 2011) and the B and T lymphocytes development (Sinkora and Butler,  
130 2016). However, we would like here to recall some important swine specific features:

131 **Myeloid cells: Neutrophil** serine proteases (NSP) have critical roles in neutrophil-associated tissue-  
132 destructive diseases. Human and mouse NSP present different peptide substrate specificities  
133 (Kalupov et al., 2009) whereas porcine NSP, present on the surface of triggered neutrophils and  
134 neutrophil extracellular traps (NETs) are efficiently inhibited by human NSP inhibitors (Bréa et al.,  
135 2012). In addition to neutrophils, porcine basophils and eosinophils can be identified by flow  
136 cytometry (Blanc et al., 2020; Haverson et al., 1994).

137 **Peripheral blood monocytes** present in pig a similar division in CCR2+/CX3CR1-/CD14+/CD163-  
138 /MHC-II- and CX3CR1+ CCR2-/CD14-/CD163+/MHC-II+ monocytes (Moreno et al., 2010). When  
139 human, mouse and porcine monocytes were compared by a transcriptomic study, porcine CD14+ and  
140 CD14- blood monocytes resembled more to their human counterparts than mouse monocytes  
141 (Fairbairn et al., 2013).

142 **Dendritic cells** (DC) subpopulations corresponding to cDC1, cDC2, pDC and moDC (Guilliams et al.,  
143 2014) can be readily identified in blood (Auray et al., 2016), skin (Marquet et al., 2014), spleen  
144 (Soldevila, personal communication), tonsils (Soldevila et al., 2018), tracheal epithelium and lung  
145 (Maisonasse et al., 2016), with minimal species-specific features. The main swine DC peculiarity is  
146 the differential expression of TLR3, which is almost exclusively expressed on pDC in swine (Auray et  
147 al., 2016; Soldevila et al., 2018) but on cDC1 in human (Poulin et al., 2010) and mouse (Desch et al.,  
148 2011). Despite this difference, the calculation of a similarity score between swine, human and mouse  
149 cDC1, cDC2 and pDC transcriptomic signatures highlighted that the three human's blood DC  
150 populations resembled more to their porcine than to their murine counterparts, especially cDC2,  
151 which appears to be the most similar between pig and man (Auray et al., 2016).

152 **Lymphoid cells:** It has long been thought that porcine B cells were generated in ileal Peyer's patches,  
153 however it is now clear that porcine B lymphopoiesis is located in the bone marrow as for other  
154 mammals (Sinkora and Sinkorova, 2014). To note, the porcine B cell development studies are still  
155 impaired because of the absence of antibodies recognizing pan-B cells markers such as CD19 and  
156 CD20 (Dawson and Lunney, 2018) and the absence of antibodies discriminating porcine IgG isotypes.  
157 Despite these difficulties, the porcine peripheral B lymphocyte differentiation steps have been  
158 described: IgM+CD2+CD21+ B cells are composed of naive B cells, IgM+CD2-CD21+ are activated or  
159 primed B cells and CD79 $\alpha$ +CD2+CD21- or CD2-CD21- represent antibody producing B cells (Sinkora et  
160 al., 2013), memory and effector antibody-forming B cells remaining CD79 $\alpha$ +CD2+CD21- while  
161 CD79 $\alpha$ +CD2-CD21- B cells are probably composed of resting plasma cells. In a recent paper (Bordet  
162 et al., 2019), we investigated the structure of the trachea-bronchial inverted porcine LN and, thanks  
163 to the conservation of the B cell affinity maturation master-genes expressions (BCL6, Pax5, IRF4,  
164 XBP1 and Blimp1), we were able to distinguish the centroblasts, centrocytes, plasmablasts and  
165 plasma cells in their respective follicular and extrafollicular LN sublocalisations, as observed in mouse  
166 and human (for review see (Klein and Dalla-Favera, 2008)). Interestingly, we also identified a specific  
167 feature of swine inverted LN which is a centroblasts-like B cell type decorated with surface CD169  
168 proteins (Bordet et al., 2019), that interact probably with perifollicular macrophages in order to  
169 capture antigens and transport them to follicular DC (fDC). This feature might be a consequence of  
170 LN inversion in pig. In the regular murine LN, naive B cells have been shown to play this antigen-  
171 transporting role (Phan et al., 2009). Follicular DC have not been described so far in pig, however  
172 they have been identified in an evolutionary close species, the sheep, and their phenotype appeared  
173 similar to murine and human fDC (Melzi et al., 2016).

174 Development of thymic  $\alpha\beta$ T cells follows mice and humans T-cell maturation model (Sinkora  
175 et al., 2013). However, it is important to note that swine possess extrathymic CD4+/CD8 $\alpha$ + T cells,  
176 that appear to be regular memory/activated peripheral CD4 T cells (Gerner et al., 2009). The  
177 peripheral blood re-expression of CD8 $\alpha$  has been endowed with no specific role. Indeed, so far the  
178 same CD4 T cell subtypes have been described in pig, namely Th1, Th2, Th17, Treg expressing the  
179 same transcription factors (respectively T-bet, GATA-3, ROR $\gamma$ T and FoxP3) than human and murine  
180 CD4 T cells (for review see (Gerner et al., 2015)). To note, in swine some clues are in agreement with  
181 a B cell activation/Th2 pathways relying more on IL13 than on IL4 (Murtaugh et al., 2009). Finally  
182 peripheral CD8 T cells expressing Eomesodermin (Eomes), a transcription factor involved in the  
183 differentiation and long-term survival of CD8 memory T cells have been described in pig like in mouse  
184 and human blood, although these cells are less numerous in swine than in human (Rodríguez-Gómez  
185 et al., 2016). Finally, by using CD27 staining, Talker *et al* were able to distinguish *bona fide* effector  
186 memory cells (CD27<sup>neg</sup>) from naive and early activated lymphocytes (Reutner et al., 2013).

187 As in other *Laurasiatheria*, pigs present a high proportion of  $\gamma\delta$  T cells (Binns et al., 1992),  
188 paralleled with more D-segments in the TCR delta gene than in human and mouse (Dawson et al.,  
189 2013). Thus porcine  $\gamma\delta$  TCR have a strong diversity potential, with no tissue-specificity (Holtmeier et

190 al., 2004) or subset restrictions (Stepanova and Sinkora, 2013) unlike in humans and mice. Moreover,  
191 conversely to murine and human ones, a consistent proportion of porcine  $\gamma\delta$  T cells retained a strong  
192 expression of GATA3 (Rodríguez-Gómez et al., 2019).

193 **Invariant NK T cells** expressed a semi-invariant TCR which recognizes glycolipids presented on the  
194 non-polymorphic CD1d molecules and corresponding either to stress-related self-ligand or to  
195 microorganism surface-antigens. Interestingly, iNKT cells frequency (Artiaga et al., 2014) as well as  
196 specific CD1d/TCR molecular interactions (Yang et al., 2019) are closer between swine and human  
197 than with mouse.

198 Conversely to the majority of mammals, swine possess an **NK cell subset** that does not  
199 express Nkp46 (Mair et al., 2012). This might be relevant here since Nkp46 recognizes  
200 hemagglutinins (HA) of influenza, parainfluenza, and Sendai virus and that its ligation leads to lysis of  
201 infected cells (Arnon et al., 2004). In swine, NKP46 expression has also been observed on CD3+ cells  
202 expressing  $\alpha\beta$  or  $\gamma\delta$  TCR but presenting the main functions of NK cells (Mair et al., 2016). Cells with a  
203 similar phenotype have been described in mice (Arnon et al., 2004) humans (Arnon et al., 2004) and  
204 cattle (Connelley et al., 2014).

205

## 206 **Specific Lung immunology**

### 207 Macrophages

208 In all mammalian species, lung macrophages are prominently composed of alveolar  
209 macrophages (AM). AM main roles are the phagocytosis of inhaled particles and the clearance of  
210 surfactant (for review see (Hussell and Bell, 2014)). AM have been shown in mouse to originate from  
211 embryonic monocytes that settled before birth in the alveoli and self-renew independently of  
212 peripheral blood adult monocytes (Guilliams et al., 2013). This scheme can be modified upon events  
213 that trigger both strong inflammation and partial or complete AM depletion. In this case, as  
214 documented in mice, recruited inflammatory monocytes will differentiate in pro-inflammatory  
215 monocyte-derived macrophages (moM $\theta$ ) before entering AM 'niche' (for review see (Guilliams and  
216 Scott, 2017)) and differentiating finally in 'true' AM, undistinguishable from the original AM  
217 population (Aegerter et al., 2020). Although not yet formally demonstrated, the belonging of human  
218 AM to the local-self-renewable macrophage type is also postulated. By analyzing AM from lung  
219 grafted patients, several teams tried to clarify the importance of AM self-renewal *versus* blood  
220 monocytes replacement in human, leading to contradictory conclusions (Bittmann et al., 2001;  
221 Eguíluz-Gracia et al., 2016; Nayak et al., 2016). However a recent work using up to date single cell  
222 technology (Byrne et al., 2020) arbitrated toward a strong contribution of blood monocytes for long  
223 term AM maintenance, the authors arguing that human beings, conversely to lab's mice, are  
224 constantly challenged by inflammatory stimuli, in a much longer time frame, and that in human  
225 everyday life, the AM pool might be replaced by moM $\theta$  within a year. In porcine lung, we observed  
226 that AM did not express blood-related genes such as cKit, CSF1R CCR2 or CX3CR1 but did expressed  
227 HDAC10, PU.1 (Bordet et al., 2018; Maisonnasse et al., 2016) whose expressions are related to  
228 embryonically-derived macrophage precursors in mouse (Guilliams et al., 2013; Schulz et al., 2012),  
229 in agreement with a similar local-self-renewable capacity of porcine and mouse AM. However,  
230 according to the 'niche theory', these local-self-renewable AM could well be former moM $\theta$  that  
231 transdifferentiated in true AM upon AM-niche occupancy as postulated in human.

232 To note, similarly to mouse and man (Keller et al., 2015), porcine AM expressed the  
233 immunoproteasome subunits LMP2, LMP7, and MECL-1 upon respiratory viral infection (Liu et al.,  
234 2018, 2017).

235 One intriguing feature of pulmonary macrophage network in swine, and the majority of the  
236 *Laurasiatheria*, is the presence of pulmonary intravascular macrophages (PIM, for review  
237 (Schneberger et al., 2012)) that are not present, at least at steady state, in mouse, rat and human

238 (Brain et al., 1999). PIM are resident lung intravascular macrophages intimately tight with endothelial  
239 cells, what differentiates them from marginated blood monocytes (for review see (Kuebler and  
240 Goetz, 2002)). We recently isolated porcine PIM and demonstrated that they were very similar to AM  
241 (Bordet et al., 2018; Crisci et al., 2020), indeed PIM and AM overexpressed genes such as PU.1 and  
242 HDAC10, leading us to suggest than PIM were, like AM, self-renewable embryonically derived  
243 macrophages, and/or that PIM may directly originate from AM (Bordet et al., 2018). PIM have been  
244 involved in acute lung inflammation in *Laurasiatheria* species (Cantu et al., 2007; Singh et al., 2004).  
245 Interestingly PIM can be induced in rat model of systemic induced inflammation triggered by biliary  
246 duct ligation (Gill et al., 2008) and some clues of PIM induction in humans suffering of liver  
247 dysfunctions (Klingensmith et al., 1978, 1976) have been reported. In a recent report using mice  
248 grafted with human bone-marrow ('humanized' mice), the authors detected PIM which were, in this  
249 model, monocyte-derived human macrophages in tight contact with murine endothelial cells (Evren  
250 et al., 2021).

251

### 252 Interstitial macrophages

253 Interstitial lung moM $\theta$  identities and functions have been recently revisited in mouse and  
254 man by the identification of two distinct populations (Chakarov et al., 2019), one Lyve1<sup>low</sup>/MHC-  
255 II<sup>high</sup>/CD163<sup>low</sup>, and the other Lyve1<sup>high</sup>/MHC-II<sup>low</sup>/CD163<sup>high</sup> respectively residing adjacent to nerve  
256 bundles and to blood vessels. The later Lyve1<sup>high</sup>/MHC-II<sup>low</sup> moM $\theta$  secreted a high basal level of IL10,  
257 supported blood vessel integrity, and decreased inflammatory cells infiltrations upon pulmonary  
258 inflammation in mice. This degree of precision has not been reached in pig, although we identified an  
259 MHC-II<sup>high</sup>/CD163<sup>low</sup>/CD169<sup>high</sup> moM $\theta$  population (Maisonasse et al., 2016) as well as an MHC-  
260 II<sup>low</sup>/CD163<sup>high</sup>/CD169<sup>low</sup> (unpublished data), whose differential roles and locations remain to be  
261 explored.

262

### 263 Dendritic cells

264 Swine DC have been identified in tonsils (Soldevila et al., 2018), tracheal epithelium and  
265 pulmonary parenchyma (Maisonasse et al., 2016). They can be divided in cDC1, cDC2 and moDC  
266 whose RNAseq signatures cluster with their mouse spleen and/or lung counterparts (Crisci et al.,  
267 2020). Plasmacytoid DC have also been identified in swine tonsil, they are E2.2 and IRF7 positive as  
268 observed in mouse and man. The porcine lung cDC and moDC populations present the functional  
269 characteristics of *bona fide* DC, migrating toward LN chemokine upon maturation, whereas only cDC,  
270 but not moDC significantly trigger naïve CD8 and CD4 T cells proliferation. Conventional DC2 are  
271 better in activating CD4 T cells than cDC1, and this in lung as well as in tonsil (Maisonasse et al.,  
272 2016; Soldevila et al., 2018), as previously described in mouse and human (Schlitzer and Ginhoux,  
273 2014). Again consistent in tonsil and in lung, both porcine cDC1 and cDC2 activate CD8 T cells,  
274 conversely to what is observed in mouse (Ng et al., 2018). Interestingly, in humanized mice, human  
275 cDC1 and cDC2 expend similarly influenza specific CD8 T cells, however only cDC2 induced mucosal  
276 effector CD8 T cells (Yu et al., 2013). This property of cDC2 has not been explored yet in swine lung.

277 Another intriguing transpecies feature of DC is the expression of Langerin on cDC2 in pig  
278 (Maisonasse et al., 2016) and human (Bigley et al., 2015) but on cDC1 in mouse (Sung et al., 2006).  
279 It has been shown in human that Langerin is rapidly induced in blood cDC2 upon TGF $\beta$  exposure  
280 (Bigley et al., 2015). Interestingly, this might be interpreted in conjunction with the expression of  
281 CD103 ( $\alpha$ E $\beta$ 7 integrin) on lung porcine cDC2, as well as with the sub-epithelial location of cDC2 in  
282 man (Yu et al., 2013) and pig (Maisonasse et al., 2016). Indeed, TGF $\beta$  is largely produced by  
283 respiratory epithelial cells and Langerin, like CD103, is induced upon TGF $\beta$  exposure (Parker et al.,  
284 1992; Picarda et al., 2016). The sub-epithelial location of cDC2 in humans and pigs might explain both  
285 the Langerin and CD103 expression phenotype and the higher involvement of cDC2 in the activation

286 of CD8 response compared with their mouse counterparts (Yu et al., 2013). FcεRIα is expressed in pig  
287 (Maisonasse et al., 2016) and human (Greer et al., 2014) but not in mouse cDC2. Indeed in mouse  
288 inflammatory moDC expressed the FcεRIα (for review see (Lambrecht and Hammad, 2012)). This  
289 difference might be of great importance in the feedback of allergic response since IgE/FcεRIα  
290 signaling in human cDC2 trigger an inhibition of the inflammatory response (Platzer et al., 2015)  
291 whereas it is thought that FcεRIα expression on mouse moDC would allow an IgE-mediated allergen  
292 presentation in a positive amplification loop. Interestingly, a recent work in mice complicated the  
293 cDC1/cDC2/moDC picture by demonstrating that upon inflammation lung cDC2 can arbor cDC1 and  
294 moDC features such as IRF8, CD64 and FcεRIα expressions (Bosteels et al., 2020). It would be  
295 interesting to investigate if these modifications stand true for human and porcine cDC2. Finally, in  
296 pig, monocyte-derived DC have been identified upon influenza infection and their phenotype and  
297 functions are compatible with inflammatory DC, harboring low migratory capacities and strong  
298 production of IL1β and IL8 upon stimulation (Maisonasse et al., 2016).

299

### 300 Innate lymphocytes

301 NK cells were shown to decrease in peripheral blood and to preferentially localize close to  
302 infected area in porcine influenza infected lung (Forberg et al., 2014), in agreement with an  
303 important role in the control of influenza infection as observed in mice (Gazit et al., 2006). The  
304 CD3+NKp46+ lymphocyte population described by Mair et al. (Mair et al., 2016) was minimally  
305 detected in spleen, blood and mediastinal LN (< 2%) but presented a higher frequency, associated to  
306 a large variability according to the animal, in lung (1% to 10%), what may suggest a role of this  
307 population in lung immune surveillance in swine. Invariant NKT (iNKT) cells binding human CD1d  
308 tetramers loaded with an α-GalCer analog have been described in the porcine lung. They are CD3 and  
309 CD44 positive but do not express Nkp46 and CD11b, and can be subdivided in three main populations  
310 expressing no, low or high levels of CD8α (Yang et al., 2017a). Interestingly, it has been shown  
311 recently that porcine iNKT cells were able to respond to influenza-exposed myeloid cells *in vitro*  
312 (Schäfer et al., 2019).

313 To our knowledge, an interesting observation has been done only in pig lung, which is the  
314 demonstration that γδ T cells were the main alveolar population able to migrate to bronchial LN  
315 (Pabst and Binns, 1995).

316

### 317 T Lymphocytes

318 As expected from mouse and man data, it has been observed in pig that parasitic *Ascaris*  
319 *suum* infection bias the lung immune response toward a Th2 response (GATA3, IL4, IL5 upregulation  
320 in the whole lung tissue) (Steenhard et al., 2009) and that *Actinobacillus pleuropneumoniae* bacterial  
321 infection triggered a Th17 immune response, as validated by the presence of antigen-specific IL17A  
322 secreting CD4 T cells (Sassu et al., 2017). Intranasal influenza vaccination triggered resident memory  
323 T cells (Holzer et al., 2018). Moreover, proliferating poly-functional Th1 (IFNγ, TNFα and IL2-  
324 secreting) and CD8 (IFNγ, TNFα-secreting) lymphocytes can be detected in the trachea-bronchial LN  
325 and the lung of influenza infected animals, from 6 to 44 days post-infection (Talker et al., 2016).  
326 Interestingly flu-specific IFNγ-secreting CD8 T cells expressed perforine and were 30 times  
327 overrepresented in the lung than in the peripheral blood. Cytokine production was dominated by T  
328 cells with an early effector phenotype or central memory phenotype (CD27<sup>pos</sup>) as observed in mice  
329 (Ballesteros-Tato et al., 2010) in agreement with the existence in porcine lung of tissue-resident  
330 memory T cells.

331

### 332 B lymphocytes

333 To our knowledge the B cell response in the porcine respiratory tract has only been  
334 addressed through nasal swabs and broncho-alveolar lavages antibody monitoring (among others  
335 (Bernelin-Cottet et al., 2019; Heinen et al., 2000)).

336

337 In conclusion, considering the respiratory immune system, mice and swine present both similarities  
338 and differences compared with human beings (Table 1), which must be consciously considered  
339 before choosing one species as an animal model for the pathogen of interest.

340

#### 341 **Model**

342 We will consider here the porcine models developed to tackle the main respiratory diseases  
343 identified by the WHO, at the exception of lung cancer. *Id est*, respiratory infections and vaccination,  
344 allergy and asthma, acute and chronic inflammations, to which we will add two short chapters on  
345 microbiota and lung graft (Table 2).

#### 346 Respiratory infections

347 Swine has been frequently used to study human respiratory pathogens naturally infecting the  
348 pigs, including, amongst others, *Mycobacterium* sp (Bolin et al., 1997; Ramos et al., 2017),  
349 *Pseudomonas aeruginosa* (Dehring et al., 1983; Luna et al., 2009), *Staphylococcus aureus* (Martínez-  
350 Olondris et al., 2010) and *Alphainfluenzavirus* (Rajao and Vincent, 2015). Alternatively, pigs can be  
351 susceptible to experimental infections of otherwise strictly human pathogens such as *Bordetella*  
352 *pertussis* (Foreman-Wykert and Miller, 2005). One of the main gap of naturally occurring respiratory  
353 infections in swine is the absence of a porcine equivalent of the human respiratory syncytial virus  
354 (RSV), a very significant pathogen in human, although an orthopneumovirus close to RSV has been  
355 recently detected in pigs (Hause et al., 2016) and might be present in France too (Richard et al.,  
356 2018). In this chapter we will expose the interest of the pig model for *P. aeruginosa*, influenza A and  
357 coronavirus infections.

358 -The bacterium *P. aeruginosa* rarely infects human lungs unless the host immune system has been  
359 impaired because of cystic fibrosis (CF), chronic obstructive disease (COPD) or ventilator-associated  
360 pneumonia. An infectious model has been developed in pig that recapitulates all the main features of  
361 this human infection, including bronchial contraction, transient increase in pro-inflammatory  
362 cytokines (IL8, IL6 and TNF $\alpha$ ), neutrophilia, neutrophil extracellular trap (NET)osis, and the secretion  
363 of massive amounts of neutrophil serine proteases leading to lung damages (Chevaleyre et al., 2016).

364 -*Orthomyxoviridae* and more specifically *Alphainfluenzavirus* (IAV) are pathogens of major  
365 importance in animal and human medicines. As recently reviewed, pig is more and more considered  
366 as an alternative model to consider with ferret and mouse, for the study of human influenza infection  
367 (Starbæk et al., 2018). Pigs are natural hosts of different strains of IAV (Kuntz-Simon and Madec,  
368 2009), presenting frequent interspecies transmissions from pig to man and the reverse (Chastagner  
369 et al., 2019a, 2019b), what underlines the proximity of swine and human IAV as well as the similarity  
370 of the respiratory systems in both species. The most frequently encountered subtypes in pigs, H1N1,  
371 H1N2 and H3N2, are the same than in humans. Besides that, the interest for the pig model is  
372 strengthened by the fact that pig is considered as a mixing vessel of human, porcine and avian  
373 influenza virus for the generation of new influenza virus reassortants (Ma et al., 2009). The  
374 susceptibility of pigs to infections with both avian and mammalian influenza virus was recently  
375 explained to some extent in a study showing that the porcine host factor ANP32A, contrary to  
376 porcine ANP32B and other mammalian ANP32, had stronger supporting activity to the avian viral  
377 RNA polymerase (Zhang et al., 2020). In pigs, IAV are responsible of mild diseases (for review (Crisci  
378 et al., 2013)) with low fever (40.5°C versus 39.5°C for normal body temperature), low inflammatory  
379 signs of the upper respiratory tract (nasal/ ocular discharge and conjunctivitis), dyspnea and

380 coughing (Talker et al., 2016) very similar to human common, mild influenza infections. In mice,  
381 which are not the natural hosts for IAV, adapted strains trigger whole lung infection and  
382 inflammation, leading to death, more similar to highly pathogenic avian influenza infections in  
383 human (Gao et al., 2013). Ferrets are recognized among the best model for testing pathogenicity and  
384 transmission of human respiratory viruses including IAV (Enkirch and von Messling, 2015), although  
385 the evolutionary reasons for this convergence are still a mystery. Interestingly, a recent comparison  
386 of influenza heterosubtypic vaccination in pigs and ferrets, showed different outcome between  
387 species and underlined the interest of using different preclinical models to assess new vaccines  
388 against flu (Holzer et al., 2018). Which animal model, the pig or the ferret, reflects best the situation  
389 in human remains however to be determined.

390 By keeping the immune response under control, AM are recognized as the 'peace-keepers' of  
391 the lung (Schneider et al., 2014). In mouse (Schneider et al., 2014) like in pig (Kim et al., 2008), AM  
392 depletion aggravate the IAV-mediated disease. In pigs, similarly to humans, disease severity has been  
393 associated with increased local pro-inflammatory cytokines (Barbé et al., 2011; Khatri et al., 2010).  
394 This cytokine storm has been associated in mice to the arrival of inflammatory moDC in the lung,  
395 indeed, pharmacological or genetic downregulation of moDC trafficking moderates the early  
396 inflammation, reduces morbidity and mortality without impacting the mounting of the adaptive  
397 immune response (Aldridge et al., 2009). This model might also stand for IAV infection in swine, since  
398 we observed the arrival of similar pro-inflammatory moDC in the porcine lung as soon as 2 days post-  
399 IAV inoculation (Maisonasse et al., 2016). As in mouse (Westerhof et al., 2019) and human  
400 (Bonduelle et al., 2014), influenza virus infections in pigs trigger multifunctional blood (Talker et al.,  
401 2015) and lung (Talker et al., 2016) antigen-specific CD8 and CD4 T cells. Interestingly a strain of  
402 inbred animals, the Babrahama pigs, allowed the use of swine major histocompatibility class I (MHC-  
403 I) tetramers to analyze the anti-NP CD8 T cells raised upon influenza intranasal vaccination (Tungatt  
404 et al., 2018), and influenza infection (Edmans et al., 2021). This last study also detected a strong  
405 influx of  $\gamma\delta$  T cells in the alveolar space during influenza infection. Similarly, and in agreement with a  
406 role in respiratory immunity, the CD3+NKp46+ lymphocyte population described in swine by Mair et  
407 al. (Mair et al., 2016) presented a strong increase in the lung of influenza infected animal, most  
408 probably due to local proliferation. SCID human beings and pigs presenting an autologous deficiency  
409 in Artemis gene (DCLRE1C) (Moshous et al., 2001) do not develop adaptive immune T and B  
410 lymphocytes but harbor functional NK cells (Powell et al., 2016). Human affected by this mutation  
411 present recurrent respiratory infections but not recorded influenza infections (Volk et al., 2015), and  
412 survived early childhood thanks to intravenous Ig therapy. Interestingly SCID/Artemis pigs presented  
413 higher virus excretion and delay in virus clearance, but milder lung lesions and clinical signs  
414 compared with their heterologous counterparts (Rajao et al., 2017), in agreement with a role of the  
415 adaptive immune response both in the control of the viremia and in the inflammatory pathology. In  
416 short, pigs can be an interesting model of human influenza infection using endemic porcine or  
417 human influenza viruses. The height of the influenza porcine model being to use pig-originated  
418 pdmH1N1 (Mena et al., 2016) human pandemic virus in porcine infectious assay as a model of the  
419 human infection (Schwaiger et al., 2019).

420 **-Coronavirus:** With the recent COVID-19 crisis there is new need for the development of relevant  
421 animal models to study coronavirus infections. In pig, the only respiratory coronavirus (Porcine  
422 Respiratory Coronavirus, PrCoV) is an *Alphacoronavirus* which is a variant of the Transmissible  
423 Gastroenteritis Virus (TGEV) (Wang et al., 2019). Indeed, a large 5' deletion in the Spike gene of TGEV  
424 altered the tropism and the virulence of PrCoV. PrCoV receptor is the aminopeptidase N (APN also  
425 named CD13), mainly expressed on respiratory and intestinal epithelial cells, whereas human SARS-  
426 CoV and SARS-CoV-2 bind to ACE2, a protein similarly expressed on respiratory and intestinal

427 epithelial cells but also on endothelial cells, which may have strong implication in virus pathogeny  
428 (Saponaro et al., 2020). Indeed, engineering transgenic mice expressing the human ACE2 suffice to  
429 trigger the full clinical picture of SARS-CoV-2 in mice (Bao et al., 2020; Israelow et al., 2020; Sun et al.,  
430 2020). Regarding the first SARS-CoV, the pig has been demonstrated to be susceptible (Chen et al.,  
431 2005). With the SARS-CoV-2, the situation is less clear and contradictory results have been reported  
432 (Meekins et al., 2020; Pickering et al., 2020; ScloTTau et al., 2020; Shi et al., 2020). In 3 out of 4 of  
433 these reports (Meekins et al., 2020; ScloTTau et al., 2020; Shi et al., 2020), pigs inoculated using nasal  
434 or oral routes did not develop any lesions nor clinical signs. Moreover, authors did not detect any  
435 viral excretion. However in one of these 3 studies (Meekins et al., 2020) SARS-CoV-2 replicated in  
436 porcine epithelial cell lines. In the fourth study (Pickering et al., 2020), mild clinical signs were  
437 observed in some inoculated pigs and viral RNA was detected in nasal lavage and oral fluid.  
438 Furthermore, infectious virus was isolated from submandibular LN in one pig 13 days post-  
439 inoculation and a serological response was evidenced in two animals 11 days post-inoculation  
440 (Meekins et al., 2020). Thus, at this early stage, it is very difficult to definitely conclude about the  
441 relevance of the pig model for the study of SARS-CoV-2.

442 The SARS-Cov-2 emergence revealed the lack of knowledge on seasonal human coronavirus.  
443 The prototype viruses from the two main HCoV lineages are 229E (*Alphacoronavirus*, like the porcine  
444 PrCOV) and OC43 (*Betacoronavirus*). They cause 15–29% of all common colds, and are the best  
445 characterized HCoV, although 2 other human coronavirus are also considered as endemic (NL63 and  
446 HKU1) (Su et al., 2016). In addition, HCOV-229E uses the same receptor as PrCOV. Thus swine might  
447 be a good model of seasonal coronavirus infections allowing, in addition, the investigation of  
448 coronavirus and IAV co-infections.

449 Regarding respiratory infections, it is worth to report here that pig lungs are suitable for the  
450 generation of precision cut lung slices (PCLS) permitting the analysis, using multiple *in vitro*  
451 conditions, of monoinfections (Delgado-Ortega et al., 2014) as well as of coinfecting viruses' complex  
452 interactions on primary tissue-samples (Dobrescu et al., 2014; Saade et al., 2020).

453

#### 454 Vaccination

455 Reviews arguing for the use of large animal models, including swine, have been published in  
456 2015 that inventoried pig usage for vaccination and challenge tests against *Bordetella pertussis*,  
457 *Chlamydia trachomatis*, human norovirus, rotavirus and IAV (Gerdtts et al., 2015; Rajao and Vincent,  
458 2015). In addition to allow the evaluation of vaccines directly through protection against an  
459 infectious challenge, animal models can permit to evaluate vaccines indirectly through immune  
460 responses measurement without the final step of the infectious challenge. In this case, the animal  
461 model is not anymore needed to be susceptible to the pathogen. For instance, swine are commonly  
462 used to assess the potency of delivery devices and adjuvants.

463 **-Delivery:** The place and mode of delivery determine the localization of memory and effector cells  
464 upon challenge. For instance it has been shown in mice that epicutaneous (EP) vaccination allows  
465 mucosal immune response in mice (Belyakov et al., 2004). Pig skin is recognized as a good model of  
466 human skin because of structure (hairiness, epidermis and dermis thickness, subcutaneous fat) and  
467 lipid composition (Hammond et al., 2000) similarities, which makes pig skin permeability similar to  
468 the human one, as well as because of dendritic cells and macrophages resemblance (Marquet et al.,  
469 2014; Summerfield et al., 2015). Thus pig is a model of choice to test EP, transcutaneous (TC) and  
470 intradermic (ID) vaccination protocols for the induction of respiratory immune protection. Direct  
471 intramuscular (IM) DNA vaccination presented early encouraging success in mouse (Ulmer et al.,  
472 1993) that were not reproduced in large animals including humans and pigs. Although not further  
473 investigated, this discrepancy might rely on tissue stiffness differences according to the animal size.  
474 Vaccination against respiratory diseases can also favor a pulmonary localized immune response by

475 directly exposing the target tissue to the antigens using aerosol (AS), intranasal (IN) or intratracheal  
476 (IT) deliveries. For that purpose, the size of swine upper respiratory tract, more similar to the human  
477 ones than small animals such as mouse or ferret, might guarantee a better compliance with clinical  
478 situations (Kirschvink and Reinhold, 2008; Rogers et al., 2008). As an illustration, herein some  
479 technics used in vaccination (mainly against influenza) in swine: prime-boost DNA/whole virus  
480 vaccine delivered ID/IM (Hewitt et al., 2019), single ID Aujeszky's Disease Virus glycoproteins vaccine  
481 (Le Luduec et al., 2016), influenza-proteins, DC-targeted ID or IM vaccination (Bernelin-Cottet et al.,  
482 2016), protein, epicutaneous anti-RSV vaccination (Hervé et al., 2016), single-cycle influenza virus  
483 delivered AS (Holzer et al., 2018), influenza virus-derived-replicon delivered IM (Ricklin et al., 2017),  
484 nanoparticules whole influenza virus encapsulation delivered IN (Dhakal et al., 2017) and aerosol  
485 intranasal delivery (Martini et al., 2020).

486 - **Adjuvant:** In addition to antigen and delivery, an essential part of a vaccine is the adjuvant used to  
487 increase the immunogenicity of dead vaccines. One of the main developing arm of adjuvant is the  
488 use of TLR-ligands, that trigger inflammation and antigen presenting cells activation. In that instance,  
489 swine present a restrictive expression of TLR3 on pDC (Auray et al., 2016; Soldevila et al., 2018)  
490 compared to the TLR3 expression on cDC1 in human (Poulin et al., 2010) and mouse (Desch et al.,  
491 2011). Conversely, pig and human, but not mouse, expressed an active TLR8 receptor that can detect  
492 RNA specifically from live bacteria (Ugolini et al., 2018), leading to a better activation of follicular DC  
493 and the differentiation of high affinity antibodies. Finally, it has been proposed to use  $\alpha$ GalSer as an  
494 adjuvant in human vaccination that would harness iNKT cells (Speir et al., 2017) and help for CD8 T  
495 cells activation. This strategy has been prospected in pig (for review (Yang et al., 2017b)). A first  
496 assay using  $\alpha$ GalSer as immunostimulant before IAV infection did not allow protection (Gu et al.,  
497 2021), although this result does not preclude the use of  $\alpha$ GalSer as true vaccine adjuvant.

498

#### 499 Microbiota

500 In the last years the importance of the microbiota and especially the gut microbiota in the  
501 preservation of homeostasis and health has been extensively studied. The gut microbiota can  
502 influence the lung health and the susceptibility of porcine host to respiratory infections (Bassaganya-  
503 Riera et al., 2003; Niederwerder, 2017). It is also known that all the mucosa in the body have some  
504 connections forming the common mucosal immune system in man (Dang and Marsland, 2019) as in  
505 pig (Wilson and Obradovic, 2020). Because of the use of pigs in biomedical research, some  
506 comparisons between human and pig gut microbiota have been carried out. By deep metagenome  
507 sequencing of faecal DNA from 287 pigs, Xiao and collaborators showed that among functional  
508 pathways found in humans, 96% were present in pigs (Xiao et al., 2016). However, in other studies  
509 comparing gut microbiota (Xiao et al., 2016) and fecal microbiota (Kobayashi et al., 2020) in different  
510 species, it was shown that pig was less close to humans than marmosets and three shrews. Moreover  
511 the pig, even if omnivorous like humans, had fecal microbiota showing some common features with  
512 herbivores as the presence of *Fibrobacter*, a cellulolytic bacterium (Kobayashi et al., 2020). Recently a  
513 further demonstration of the gut lung axis has been demonstrated in swine with an impact of a  
514 porcine herpesvirus (Aujeszky's Disease Virus) on microbial community and immune status in the  
515 ileum and colon of piglets (Zhang et al., 2019). Finally, the last decade firmly established the  
516 existence and precisely described a symbiotic, stable respiratory microbiota in mouse and man (for  
517 review see (Man et al., 2017). These investigations remain to be done in pig.

518

#### 519 Respiratory Allergy and Asthma

520 Respiratory allergy corresponds to the improper activation of a Th2 response, leading to the  
521 establishment of an IgE mediated anamnestic immune response that will trigger eosinophils

522 degranulation and asthma. Although food allergy is well-established in swine (for review see (Rupa et  
523 al., 2009)), allergic asthma does not occur spontaneously in the animal world, albeit guinea pigs,  
524 ferrets and pigs can be artificially sensitized. The establishment of a stable chronic porcine asthma  
525 model appears to be difficult because the sensitivity to the antigen declines after repeated allergen  
526 exposure (Szelenyi, 2000). However, upon *Ascaris suum* antigen sensitization consisting of an *A.*  
527 *suum* extract in Al(OH)<sub>3</sub> followed by two booster doses and a challenge with nebulized allergen, pigs  
528 developed airway inflammation associated with eosinophils and neutrophils infiltration (Fornhem et  
529 al., 1996). On the induction side, cDC2 have been demonstrated to be the main trigger of the Th2  
530 bias involved in the allergic response. As specified in the dendritic cells chapter above, porcine cDC2  
531 resemble more to human than to mice cDC2 on several aspects in blood (Auray et al., 2016) as well  
532 as in the respiratory tract (Crisci et al., 2020). For instance, the two main features important to recall  
533 here are the expression by cDC2 of the FcεR1α, a receptor of IgE, and the intra-epithelial and sub-  
534 epithelial cDC2 location in the trachea and the bronchia respectively (Maisonnasse et al., 2016; Yu et  
535 al., 2013). Invariant NKT cells have been strongly involved in the Th2 bias of allergic responses (for  
536 review see (Matangkasombut et al., 2009)), interestingly Renukaradhya *et al.* demonstrated that  
537 intra-tracheal instillation of α-GalCer analog in pigs triggered iNKT cells activation and acute airway  
538 hyperactivity associated with a Th2 cytokine profile (Renukaradhya et al., 2011). On the effector side,  
539 dendrograms indicate that porcine IgE is more similar to IgE of carnivores, horses and humans than  
540 to other artiodactyls IgE (Butler et al., 2009). In swine as in human, mast cell tryptase inhibitor  
541 administrated prior to allergen challenge prevented acute bronchoconstrictive response and  
542 decreased histamine release (Ploeg et al., 2002), while corticoid administration decreased airways  
543 inflammatory cells infiltration (Fornhem et al., 1996). Still on the clinical side, porcine lung smooth  
544 muscles reactions to inflammatory stimuli are a current model of asthma-muscle contraction (Ram-  
545 Mohan et al., 2020; Sieck et al., 2019). Interestingly, airway contractions upon *in vivo* acid treatment  
546 in piglets (Reznikov et al., 2019) recapitulated the airway hyper-responsiveness (AHR) gender bias  
547 observed in infants (Van Merode et al., 2007).

548 Several intravenously administered compound such as nanomedicines, radiologic contrast agents  
549 and other pharmaceutical products may trigger in human rare events of pseudoallergic infusion  
550 reactions which are hypersensitivity reactions. Thanks to their high sensitivity, pigs have been used  
551 for decades to detect such reactions, using the “complement activation-related pseudoallergy”  
552 (CARPA) model (for review (Szebeni and Bawa, 2020)). Interestingly, pig high sensitivity seems  
553 strongly related to the presence of constitutive PIM (Csukás et al., 2015), what might be a clue of the  
554 presence of induced PIM in humans susceptible to such reactions.

555

#### 556 Acute and Chronic inflammations

557 Acute lung injury (ALI) and its severe form acute respiratory distress syndrome (ARDS) are  
558 responsible for more than 10% of intensive care unit admissions. ARDS conditions can be artificially  
559 reproduced in swine by using lung repeated lavages, and oleic acid or endotoxin instillations (for  
560 review see (Ballard-Croft et al., 2012)). Porcine models more related to human medical conditions  
561 have been developed recently such as hemorrhagic shock (Morris et al., 2020), hyperoxia (Katalan et  
562 al., 2017) or ricin induced-ARDS (Katalan et al., 2017). To our knowledge, no porcine model of ARDS  
563 triggered upon infection-induced pneumonia has been reported. The early ARDS stage is  
564 characterized by an acute inflammatory response that includes release of IL1, TNF, IL8 and  
565 subsequent neutrophil recruitment (for review see (Ware, 2006)), that can be mimicked in pig  
566 (Morris et al., 2020).

567 In developed countries, chronic obstructive disease (COPD) is mostly provoked by smoking  
568 and result in the remodeling and narrowing of small airway associated with pulmonary emphysema,

569 likely due to chronic inflammation leading to increased numbers of neutrophils, macrophages, DC, T  
570 and B lymphocytes. Chronic inflammation is maintained by macrophages and neutrophils infiltration  
571 although autoimmunity related to autoantibodies and activated CD8 is suspected (for review see  
572 (Caramori et al., 2016)). The emphysema appears to be linked to metalloproteinases (MMP) catalytic  
573 activity. A mutated-pig phenotype has been described presenting emphysema associated with MMP9  
574 and 12 hyper-expression which might be the first step toward the development of a COPD porcine  
575 model (Bruun et al., 2013). To note, pigs are already used as model for cigarette smoke short (Gilman  
576 et al., 1981) and middle (Gilman et al., 1981) term effects. The development of pig as a COPD model  
577 would allow to explore an interesting hypothesis linking COPD and non-alcoholic fatty liver diseases  
578 (Lonardo et al., 2017) that we would like to bring together with the potential pro-inflammatory PIM  
579 induction in humans suffering of liver dysfunctions (Klingensmith et al., 1978, 1976). Whether the  
580 constitutional presence of PIM in swine might favor or impaired this model remains to be  
581 established.

582

### 583 Lung graft

584         Herein we will not tackle the field of xenotransplantation, that is beyond the scope of this  
585 review and has been reviewed recently elsewhere (Burdorf et al., 2018). Regular lung transplantation  
586 is the final treatment option for patients presenting end-stage lung diseases. The 1-year survival has  
587 greatly improved in the last 40 years, reaching now 84% (Chambers et al., 2017). Pig is used as a  
588 model of lung transplantation (Mariscal et al., 2018) to study primary graft dysfunctions and test new  
589 preventive interventions to reduce or avoid these conditions (Iskender et al., 2016; Martins et al.,  
590 2004). Interestingly, pig lungs are currently used to improve and further develop the promising *ex*  
591 *vivo* lung perfusion (EVLV) method (for review (Tane et al., 2017)) leading to the reconditioning of  
592 lung graft rejected in first instances because of not reaching the graft quality criteria. Porcine model  
593 allowed to validate methods that decreased the expression of acute lung injury related genes  
594 (Dromparis et al., 2019) or that increased the extracorporeal surviving time (Hozain et al., 2020).  
595 Moreover, EVLP development give accessibility and time for intervention on the lung graft before  
596 grafting. The pig model allows to test extracorporeal intervention such as IL10 gene-therapy in order  
597 to act specifically on the immune tolerability of the transplant (MacHuca et al., 2017).

598

### 599 **Conclusions and perspectives:**

600         In conclusion, we think that the development of pig as a respiratory model of medical  
601 conditions might be encouraged following three main research fields:

602         Because of the resemblances between porcine and human cutaneous, respiratory and  
603 intestinal systems, associated to the immunological similarities of these species, pig appears to be a  
604 model of choice to study the interactions between the different mucosae. In this perspective, a  
605 better knowledge of porcine skin, lung and intestinal microbiota will be needed.

606         The second important point would be to develop pig as a model of respiratory allergies  
607 according to the high similarity of cDC2 in pig and man, as well as to the good knowledge of porcine  
608 neutrophils and iNKT cells. The main immunological hurdle for this development remains the lack of  
609 reagents to follow the B cell response (B cells markers, such as CD19 and CD20 and tools to  
610 discriminate the different IgG isotypes).

611         Finally, according to the large knowledge accumulated on the pig blood monocytes and  
612 respiratory macrophages, as well as to the relative long life span of pigs, the long term consequences  
613 of immune system alterations triggered by immunostimulants or primary infections, leading to  
614 trained immunity (Angulo et al., 2020; Guillon et al., 2020; Stylianou et al., 2019; Yao et al., 2018) or  
615 tolerance (Bouras et al., 2018; Didierlaurent et al., 2008) might be advantageously studied in this  
616 model.

617 To summarize, thanks to the knowledge and tools developed during the last years, pig  
618 appears now as the third medical model after mice and non-human primates, and might be seriously  
619 considered when looking for a respiratory experimental model, especially in the fields of mucosal  
620 interactions, allergies and trained immunity.

621

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**Table I: Immune-related respiratory tract remarkable features of mouse, human and pig**

	<i>Mouse</i>	<i>Human</i>	<i>Pig</i>	<i>Comments</i>
<i>Airways</i>	-Muzzle	-Nose	-Snout	<b>-hm ≠ pg ≠ ms</b> ≠ in higher respiratory tract size and structure
	-Small airways and lungs	-Large airways and lungs	-Large airways and lungs	<b>-hm &amp; pg ≠ ms</b> ≠ in lower respiratory tract accessibility
<i>Lymph nodes</i>	-Centripetal circulation	-Centripetal circulation	-Centrifugal circulation	<b>-hm &amp; ms ≠ pg</b> no known consequences
	-Lymphocytes exit through efferent lymphatics	-Lymphocytes exit through efferent lymphatics	-Lymphocytes exit through HEV	<b>-hm &amp; ms ≠ pg</b> no known consequences
<i>Granulocytes</i>	-Neutrophil serine proteases not-sensitive to human inhibitors	-Neutrophil serine proteases sensitive to human inhibitors	-Neutrophil serine proteases sensitive to human inhibitors	<b>-hm &amp; pg ≠ ms</b> ≠ in tissue inflammation handling
<i>AM</i>	-Embryonic origin	-Probably of embryonic origin	-Probably of embryonic origin	<b>-hm=ms=pg</b>
	-Self-renew -Inflammation, replacement by moAM	-No data -Large part of moAM	-No data -No data	
<i>PIM</i>	-No information	-Induced PIM upon liver conditions?	-Constitutive inflammatory PIM	<b>-hm &amp; ms ≠ pg</b> high susceptibility of pigs to infused particles
<i>moM0/ interstitial M0</i>	-2 populations: nerve-associated blood vessel associated	-2 populations: nerve-associated blood vessel associated	-2 populations: location not explored	<b>-hm=ms=pg</b>
<i>DC</i>	-TLR3 expressed on cDC1	-TLR3 expressed on cDC1	-TLR3 expressed on pDC	<b>-hm &amp; ms ≠ pg</b> ≠ dsRNA response?
	-cDC1 mainly involved in T CD8 activation	-cDC1 and cDC2 involved in T CD8 activation	-cDC1 and cDC2 involved in T CD8 activation	<b>-hm &amp; pg ≠ ms</b> ≠ T CD8 induction?
	-cDC2 FcεRIα-, Lang-, CD103-, interstitial location	-cDC2 FcεRIα+, Lang+, CD103+, subepithelial location	-cDC2 FcεRIα+, Lang+, CD103+, subepithelial location	<b>-hm &amp; pg ≠ ms</b> ≠ allergy induction?
<i>NK/NKT cells</i>	-NKp46 specifically expressed on NK cells	-NKp46 specifically expressed on NK cells	-NK subset NKP46-, T lymphocyte subset NKP46+	<b>-hm &amp; ms ≠ pg</b> no known consequences
<i>T Lymphocytes</i>	-CD4 T cells devoid of CD8 expression	-CD4 T cells devoid of CD8 expression	-CD8α on memory CD4 T cells	<b>-hm &amp; ms ≠ pg</b> no known consequences
	-Low proportion of γδ T cells	-Low proportion of γδ T cells	-High proportion of γδ T cells	<b>-hm &amp; ms ≠ pg</b> ≠ innate immune response?
<i>B Lymphocytes</i>	-Naïve B cells transporting antigens to fDC	-Not described	-Centroblasts transporting antigens to fDC?	<b>-hm &amp; ms ≠ pg</b> no known consequences

HEV: High-Endothelial Venules; AM: Alveolar Macrophage; PIM: Pulmonary Intravascular Macrophage; moAM: monocyte-derived AM; M0: Macrophages, moM0: monocyte derived Macrophage; DC: Dendritic Cell; cDC: conventional Dendritic Cell; pDC: plasmacytoid Dendritic Cell; fDC: follicular Dendritic Cell; NK: Natural Killer; hm: human; ms: mouse; pg: pig. Bibliographic references are in the main text.

**Table 2: Non-transmissible respiratory diseases pro and con of the porcine model**

	PROS	CONS	
<b>RESPIRATORY INFECTIONS</b>	<i>B. pertussis</i>	-naturally infected	
	<i>Mycobacterium sp</i>	-naturally infected	
	<i>S. aureus</i>	-naturally infected	
	<i>P. aeruginosa</i>	-naturally infected	
	<i>Influenzavirus</i>	-natural sensitivity to human and swine strains with mild clinical signs	-no example of highly pathogenic infections
	<i>Coronavirus</i>	-natural porcine <i>αCoronavirus</i> (PrCoV) similar to the human seasonal HCoV-229E	-disputed sensitivity to SARS-CoV-2
	<i>Orthopneumovirus</i>	-natural porcine <i>Orthopneumovirus?</i>	-not sensitive to hRSV
<b>VACCINATION</b>	Delivery	-skin structure -upper respiratory tract structure	
	Adjuvant	-functional TLR8 -cDC1 interstitial and cDC2 intra-subepithelial locations -αGalSer response	-TLR3 expression on pDC not on cDC1
<b>MICROBIOTA</b>		-omnivorous species -intestinal microbiota similar to herbivore - data paucity on porcine respiratory microbiota	
<b>RESPIRATORY ALLERGY AND ASTHMA</b>	Induction	-cDC2 location -cDC2 expressing IgE receptor (FcεRIα)	-no stable chronic allergic asthma porcine model
	Clinical signs	-IgE similar to human -lung smooth muscles porcine model -efficacy of tryptase inhibitors	
<b>ACUTE AND CHRONIC INFLAMMATIONS</b>		-model of early inflammatory ARDS responses -constitutive PIM	-no infectious model of ARDS induction -constitutive PIM
	<b>LUNG GRAFT</b>	-size allowing similar surgical intervention -primary graft dysfunction model - <i>ex vivo</i> lung perfusion model	

SARS: Severe Acute Respiratory Syndrome; hRSV: human Respiratory Syncytial Virus; cDC: conventional Dendritic Cell; pDC: plasmacytoid Dendritic Cell; ARDS: Acute respiratory distress syndrome; PIM: Pulmonary Intravascular Lymphocyte. Bibliographic references are in the main text.