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Assessment of toxicity to food contaminants as mycotoxins in pigs: development and use of ex vivo organ culture models as an alternative to animal experimentation.

Delphine Payros

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➤ Assessment of toxicity to food contaminants as mycotoxins in pigs: development and use of *ex vivo* organ culture models as an alternative to animal experimentation.

Delphine Payros, Séminaire du réseau HOLO-AE, Paris, 17 décembre 2024

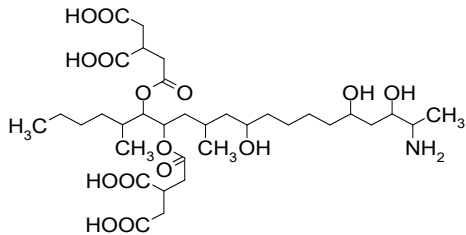


➤ “ Tout est bon dans le cochon. ”

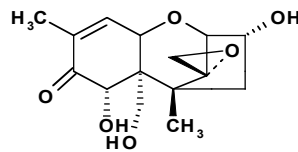
Delphine Payros, Séminaire du réseau HOLO-AE, Paris, 17 décembre 2024

➤ Mycotoxins - generalities

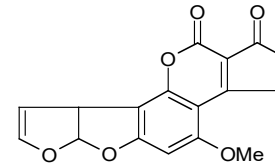
- Fungal secondary metabolites that exert toxic effects on animals and human
- More than 1000 mycotoxins have been described
- The chemical structure of mycotoxins is very diverse
- Chemical structure and toxic properties of mycotoxins are conserved during both storage and processing/cooking of food or feed



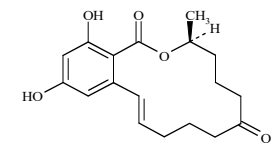
Fumonisin B1



Deoxynivalenol - DON

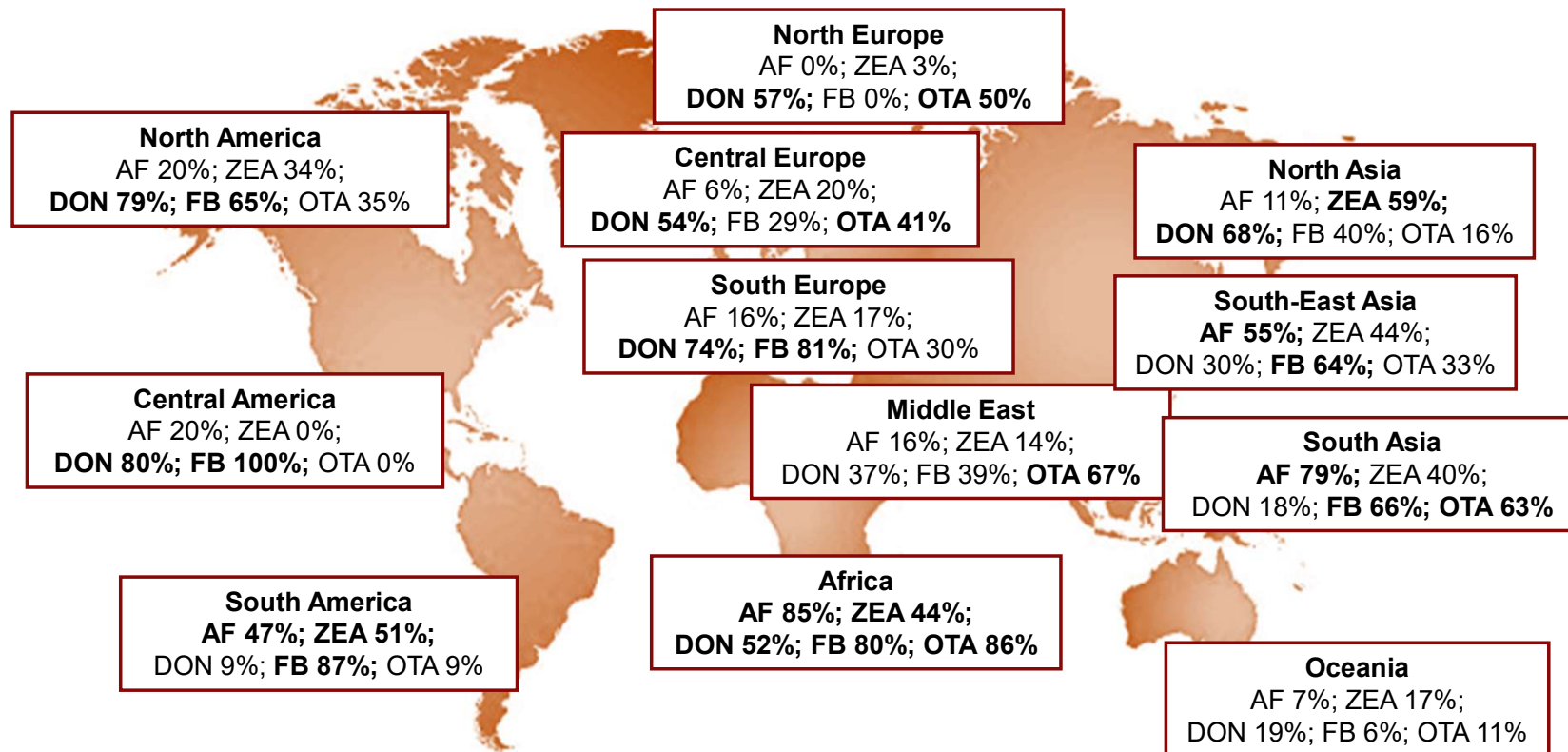


Aflatoxin B1



Zearalenone

➤ Mycotoxins : a global threat



60-70% of raw materials are contaminated



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« Tout est bon dans le cochon. »

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➤ Multiple effects of mycotoxins on pigs



Pig

- Pigs are very sensitive to mycotoxins
- High percentage of cereals and their by-products are contaminated by mycotoxins in pig diet
- Important economical losses in farms and industries

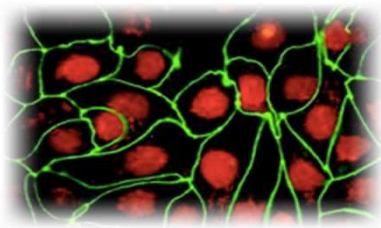
Symptoms	Mycotoxins					
	AFB1 AFB2	OTA	DON	T2 HT2	FB1 FB2	ZEN
Anorexia	+	+	+++	+++	+	
Growth	+++	+	+++	++	+	
Liver damage	+++	+			++	
Kidney damage		+++			+	
Abortion					+	++
Infertility						+++
Vulvovaginitis						+++
Pulmonary oedema					+++	
Immunomodulation	+++		++	++	+++	+

Deoxynivalenol

➤ Models to investigate the intestinal response on pigs



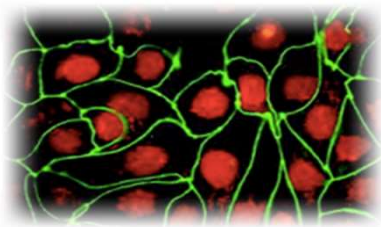
In vitro epithelial cells



- Single cell type
- Mechanistic analysis
- Limited cell complexity

➤ Models to investigate the intestinal response on pigs

In vitro epithelial cells



- **Single cell type**
- Mechanistic analysis
- Limited cell complexity

Ex vivo intestinal explants

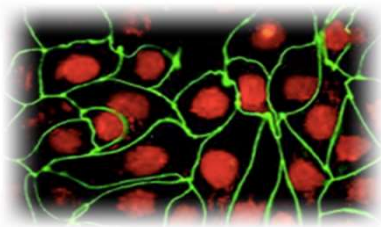


- **Intact tissue**
- reduction in the number of animals
- increased repetitions

➤ Models to investigate the intestinal response on pigs



In vitro epithelial cells



- Single cell type
- Mechanistic analysis
- Limited cell complexity

Ex vivo intestinal explants



- Intact tissue
- reduction in the number of animals
- increased repetitions

In vivo in pigs



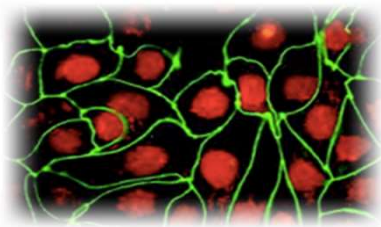
- representative of cell complexity
- Long and expensive
- Limited repetition number



➤ Models to investigate the intestinal response on pigs



In vitro epithelial cells



- Single cell type
- Mechanistic analysis
- Limited cell complexity

Ex vivo intestinal explants

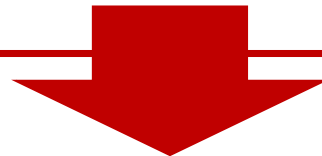


- Intact tissue
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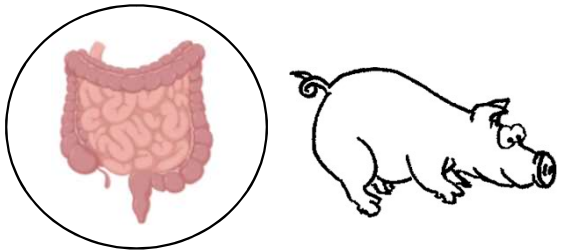
In vivo in pigs



- representative of cell complexity
- Long and expensive
- Limited repetition number



➤ Use jejunal explant to test solutions for improving pig health



Reduce the action of the mycotoxin

Jejunal explant culture



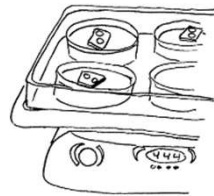
Probiotics/Postbiotics

+

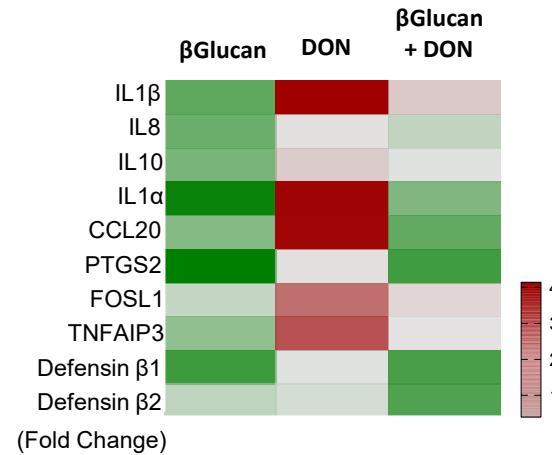
Mycotoxins

(ex: deoxynivalenol, DON)

Co-exposure



DON + β -glucans



Modulation of pro- and anti-inflammatory gene expression

Marquis, ..., Payros et al., Journées pour la Recherche Porcine, 2023

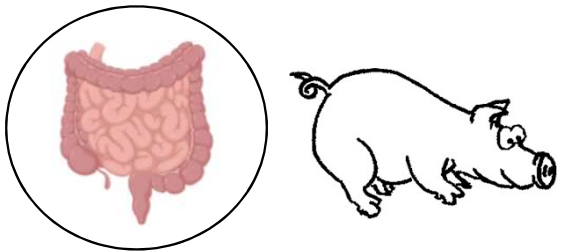


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➤ Use jejunal explant to test solutions for improving pig health



Jejunal explant culture



Probiotics/Postbiotics

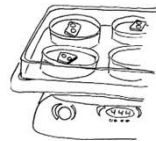
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Mycotoxins

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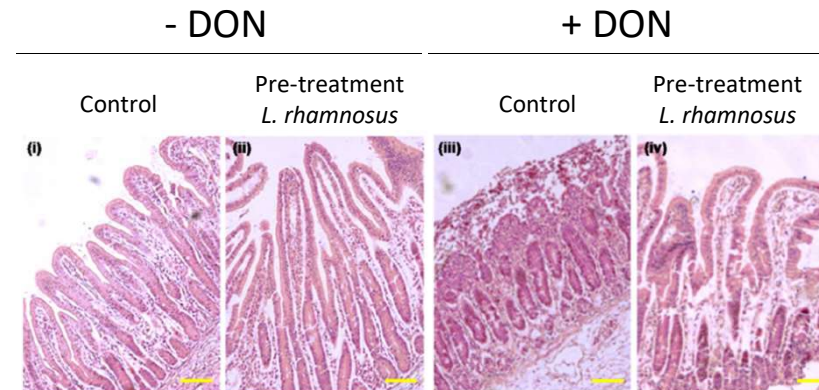
Reduce sensitivity to their toxic effects

Pre-treatment



Lactobacillus rhamnosus

DON exposure



↘ Histomorphological damage



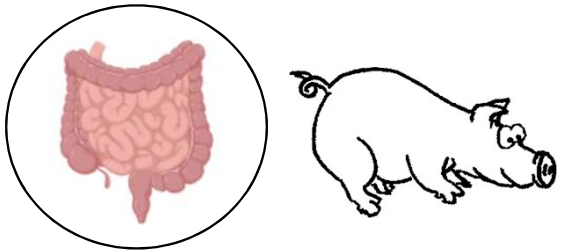
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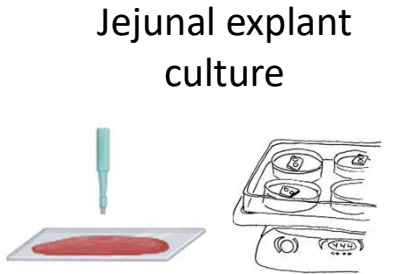
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Payros*, Garcia*, et al. Arch. toxicol., 2018 p. 11

➤ Use jejunal explant to test solutions for improving pig health



Reduce sensitivity to their toxic effects

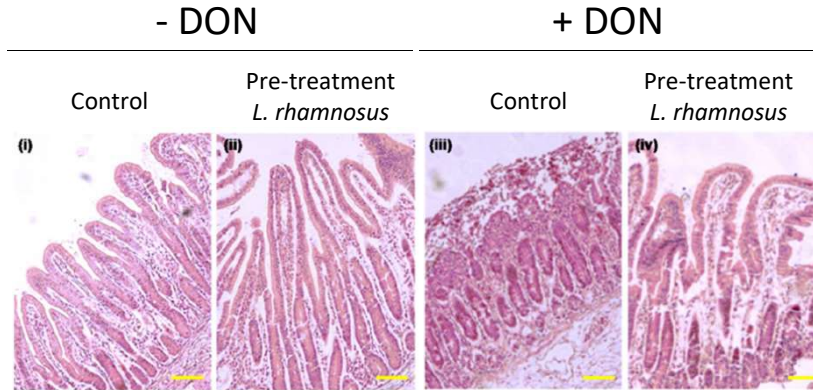


Pre-treatment



Lactobacillus rhamnosus

DON exposure

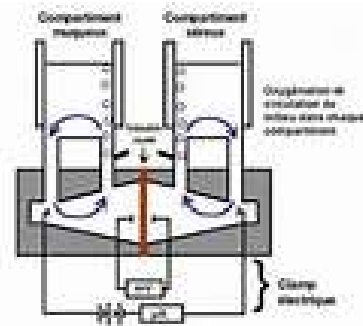


Probiotics/Postbiotics

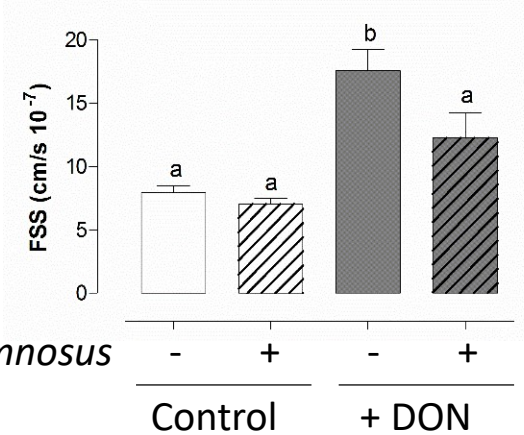
+

Mycotoxins

(ex: deoxynivalenol, DON)



Ussing chambers



↘ Histomorphological damage
↘ Paracellular permeability to FSS



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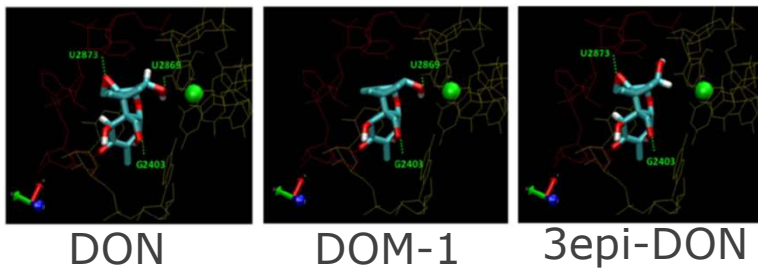
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Payros*, Garcia*, et al. Arch. toxicol., 2018 p. 12

➤ Deoxynivalenol is metabolized by bacteria in the microbiota to less toxic metabolites



Bacterial biotransformation of DON to DON metabolites with reduced toxicity.



Absence of the epoxy group decreases the affinity of DOM-1 and 3epi-DON and prevents the induction of ribotoxic stress

Pierron et al., Scientific reports, 2016



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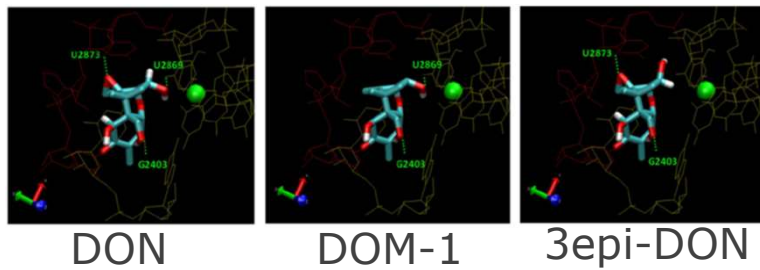
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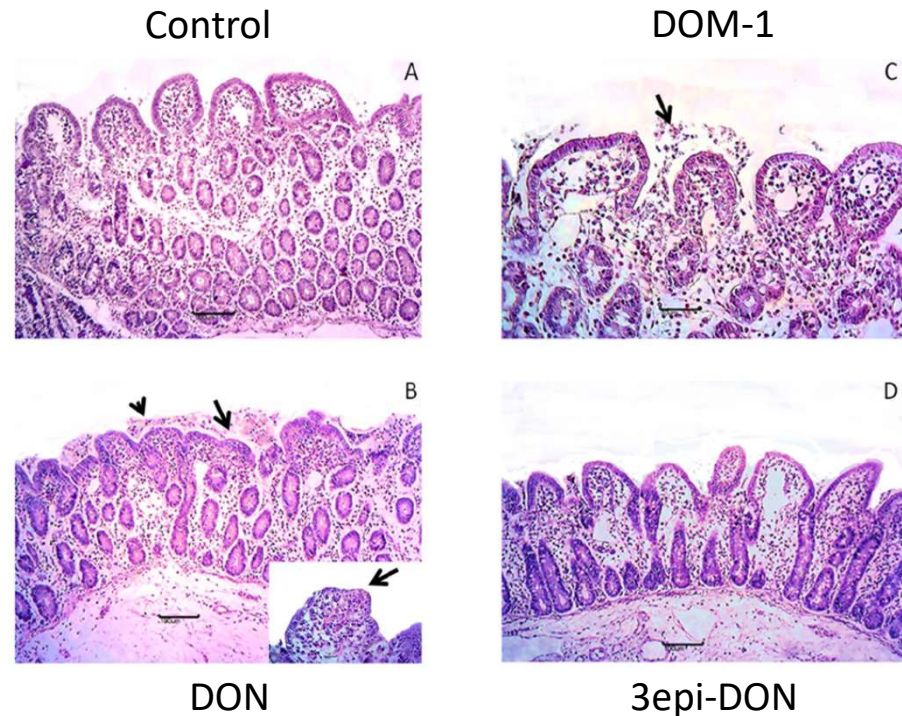


Bacterial biotransformation of DON to DON metabolites with reduced toxicity.

Pig jejunal explants exposed 4 h to CTRL, DON & DOM-1 (3 epi DON)



Absence of the epoxy group decreases the affinity of DOM-1 and 3epi-DON and prevents the induction of ribotoxic stress



Pierron et al., Scientific reports, 2016



➤ Deoxynivalenol is metabolized by bacteria in the microbiota to less toxic metabolites



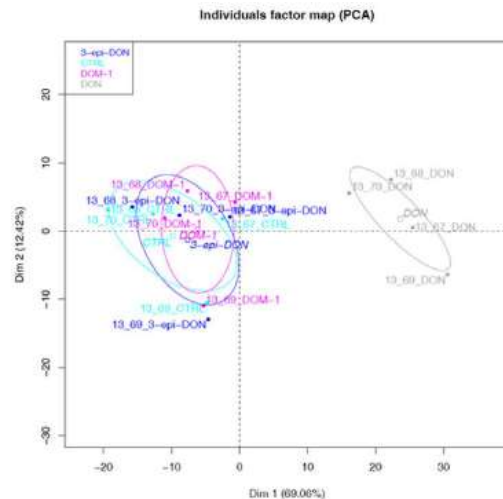
Pig jejunal explants exposed 4 h to CTRL, DON & DOM-1 (3 epi DON)

Microarray (Agilent, 60 000 probes)



34 775 probes expressed in the intestine

Principal component analysis



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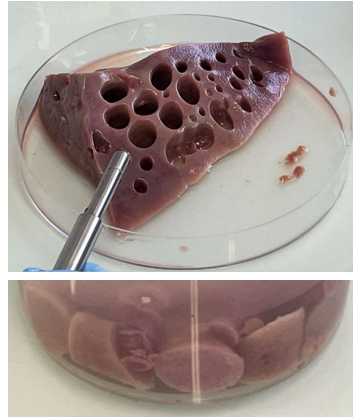
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➤ Models to investigate the hepatic response in pigs: the liver slices

Liver

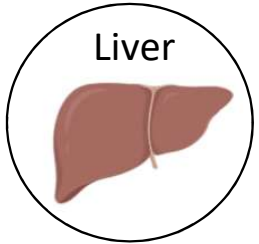


liver lobe removal

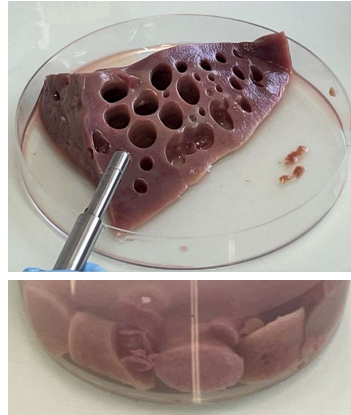


Tissue slicer
Slice 250 μ M

➤ Models to investigate the hepatic response in pigs: the liver slices

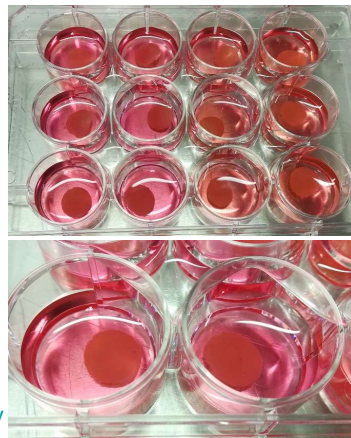


liver lobe removal

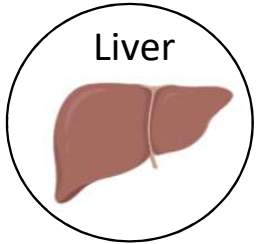


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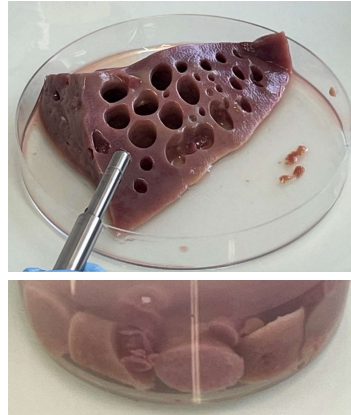
Culture from 4h to 72h



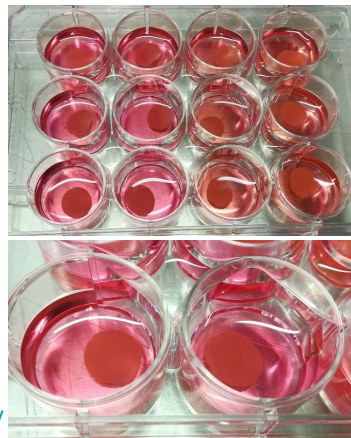
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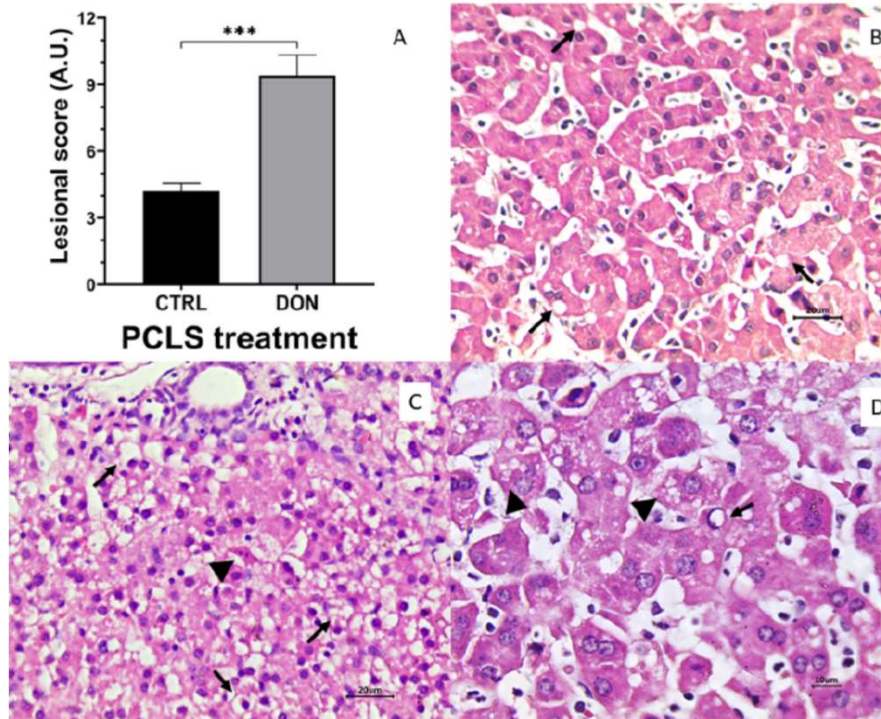
➤ Models to investigate the hepatic response in pigs: the liver slices

Exposure 4h to DON

Control

DON exacerbates hepatic cellular damage.

- ➔ Cytoplasmic vacuolation
- ▲ Cytoplasmic and nuclear vacuolation



DON Exposure

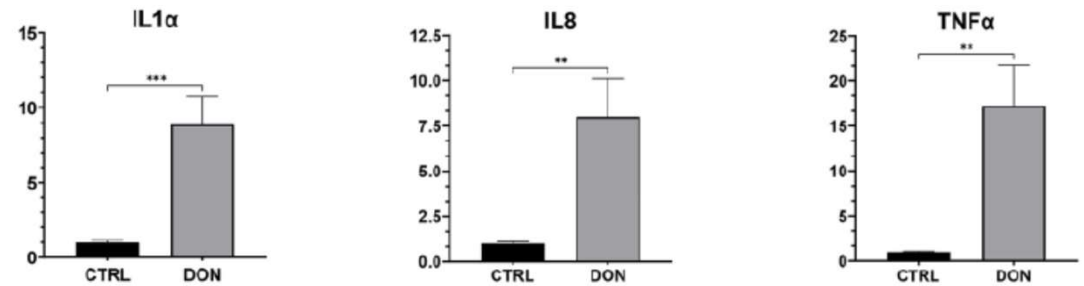
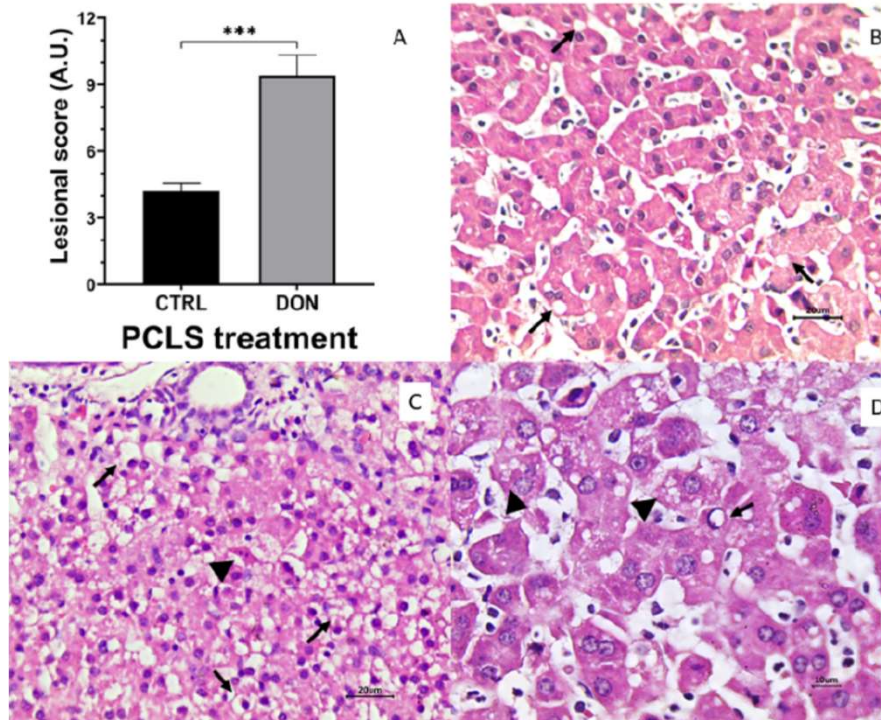
➤ Models to investigate the hepatic response in pigs: the liver slices

Exposure 4h to DON

Control

DON exacerbates hepatic cellular damage.

- ➔ Cytoplasmic vacuolation
- ▲ Cytoplasmic and nuclear vacuolation



DON exacerbates pro-inflammatory gene expression in liver slices.

DON Exposure

➤ Advantages and limits

Advantages

- Tissular structure
- Multiple readouts (gene expression, histological analysis, functional analysis, protein and cytokine abundance, ...)
- Multiple organs
- No restricted materials → For certain organs: no live animals used
- Xenobiotic, toxic and bacterial interaction



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➤ Advantages and limits

Advantages

- Tissular structure
- Multiple readouts (gene expression, histological analysis, functional analysis, protein and cytokine abundance, ...)
- Multiple organs
- No restricted materials → For certain organs: no live animals used
- Xenobiotic, toxic and bacterial interaction

Limits

- Time of conservation (intestine)
- Absence of vascular system and systemic immune system
- No zootechnical performances
- Few studies in the presence of microbiota
- Always requires of animals

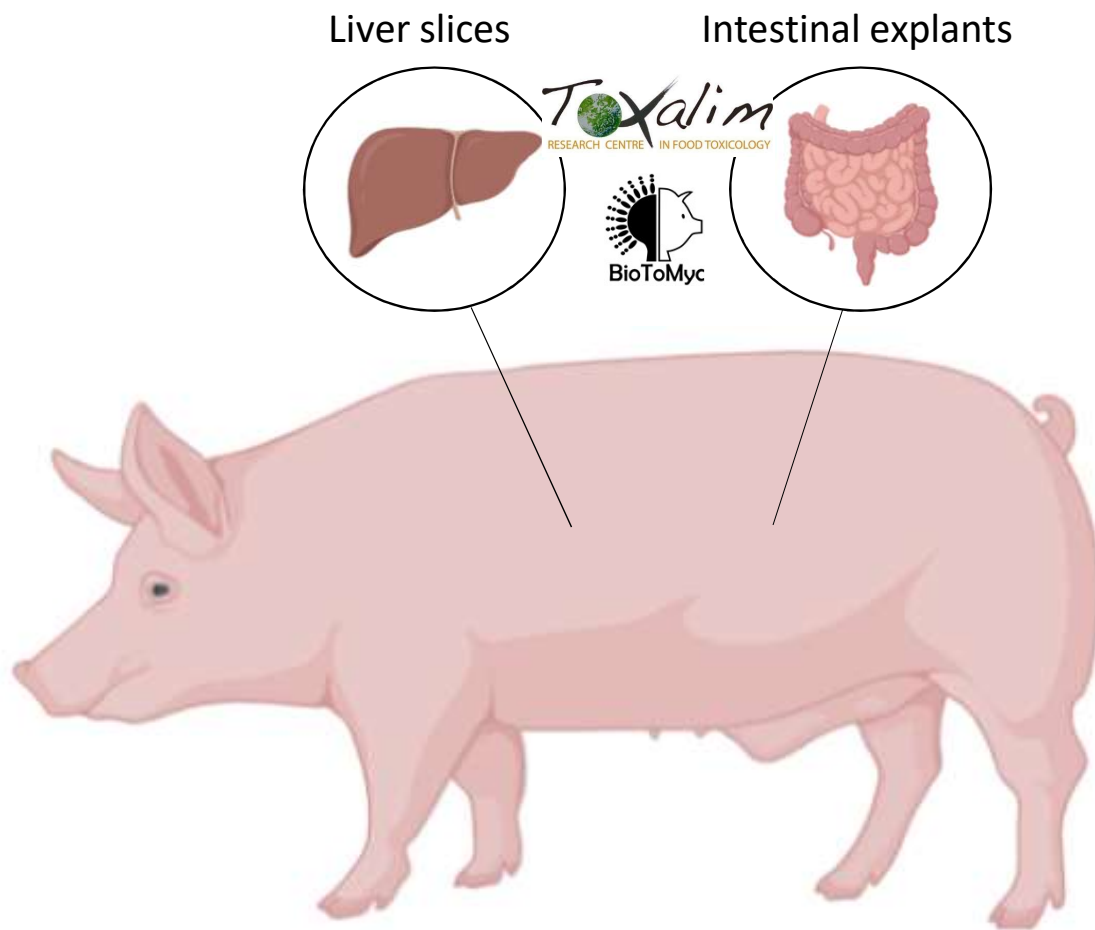


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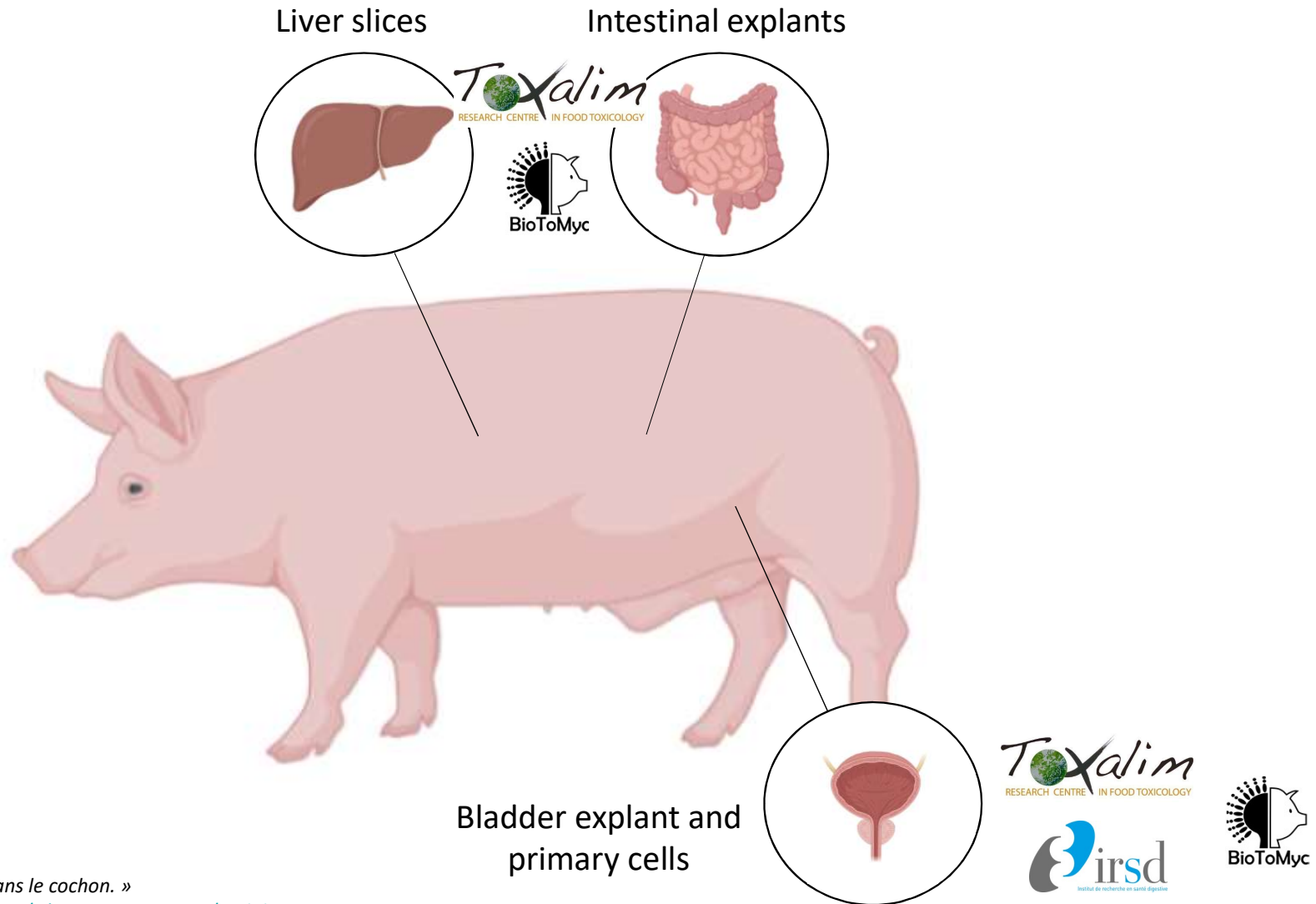
« Tout est bon dans le cochon. »

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➤ BioToMyc Team explores the toxicity of mycotoxins through several models in pigs



➤ BioToMyc Team develops new alternatives models to evaluate the toxicity of mycotoxins

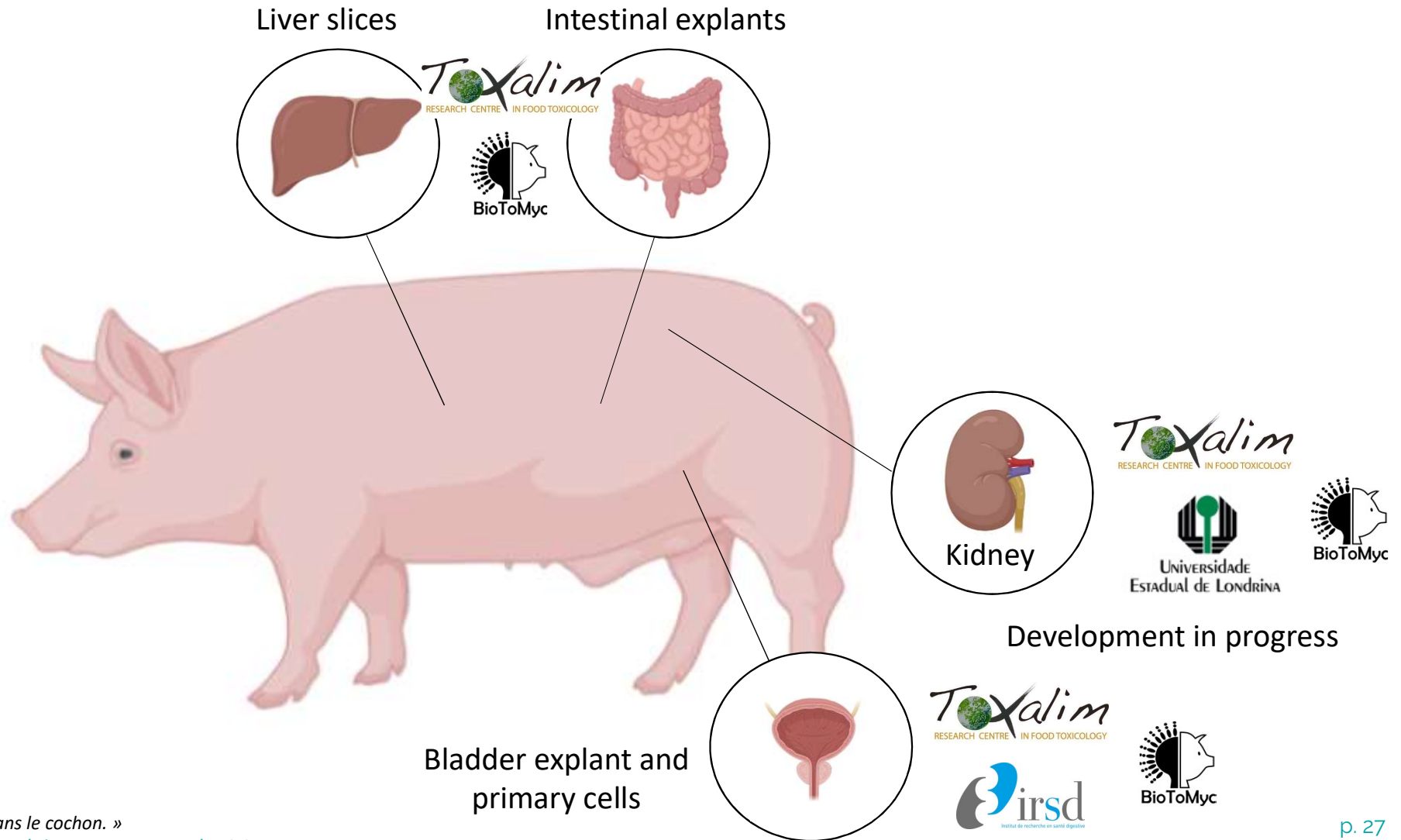


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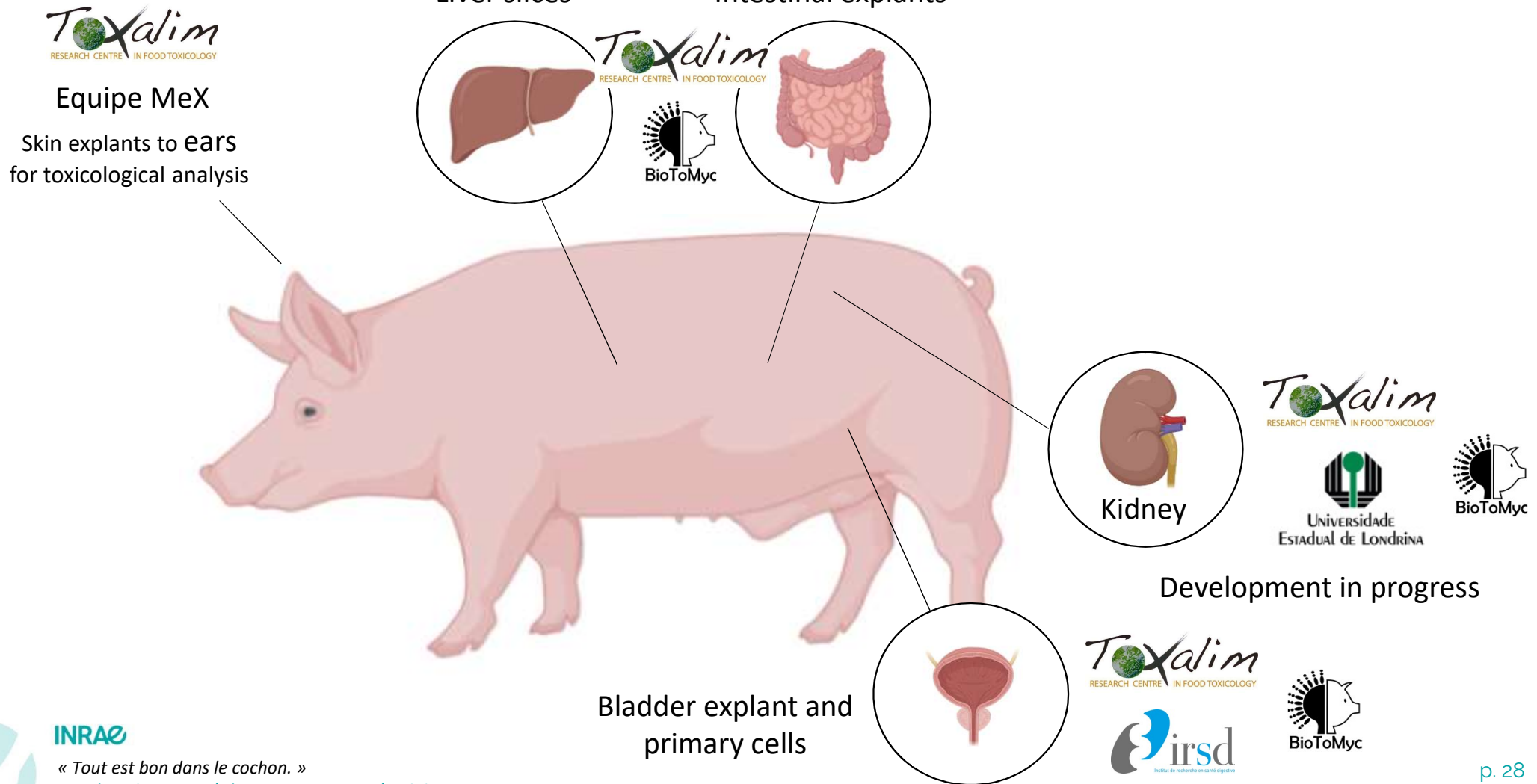


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Collaborations of the BioToMyc Team: alternative models to animal experimentation in pig

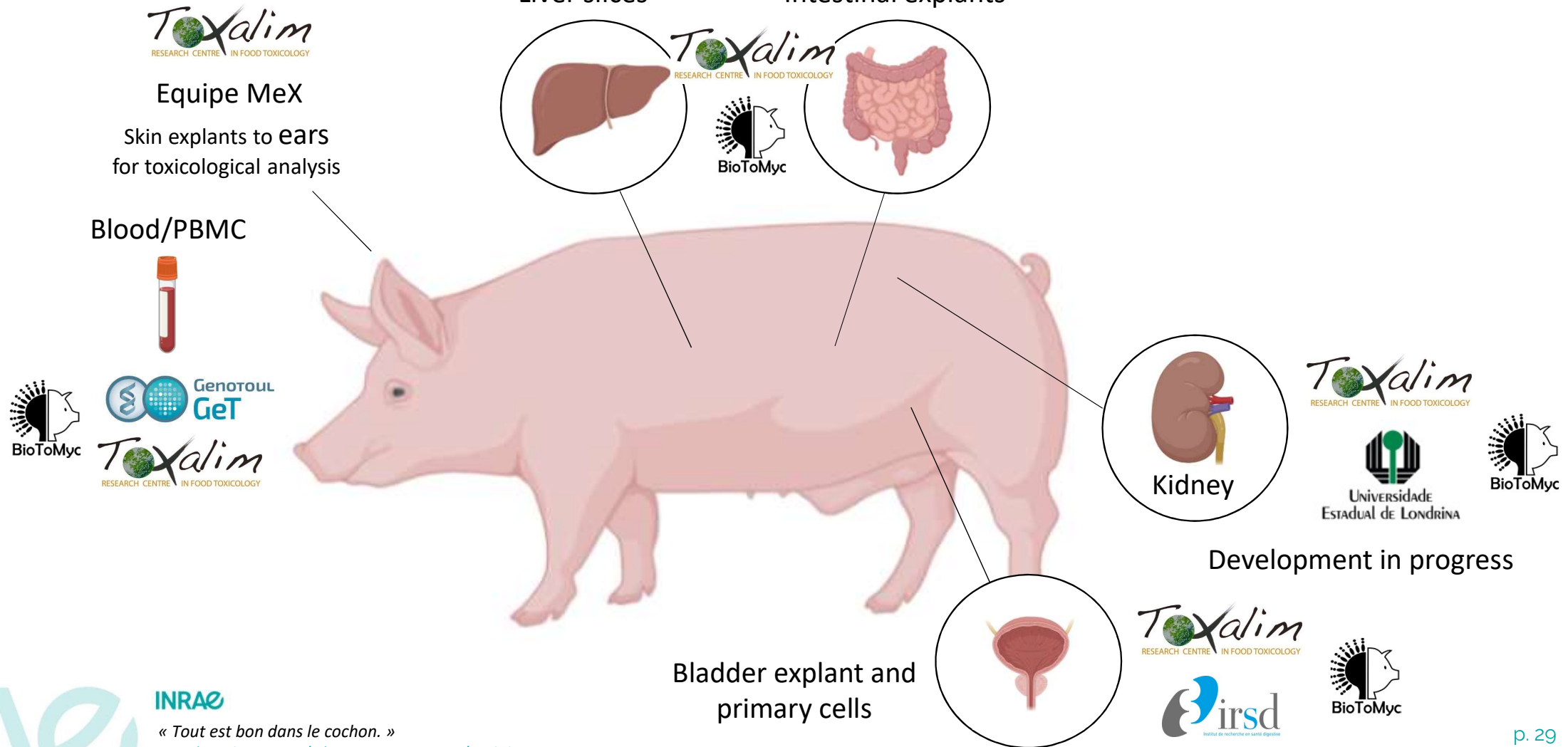


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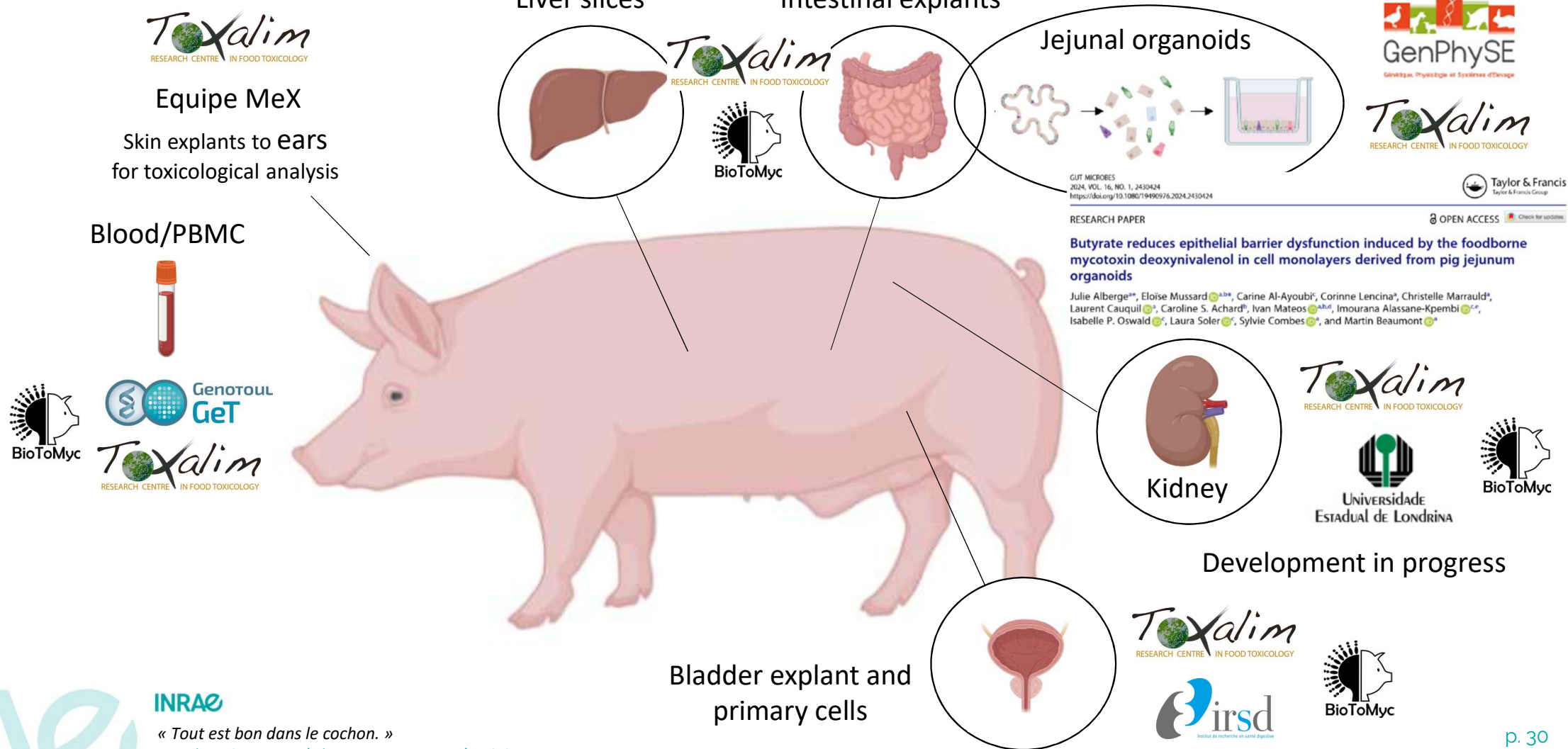


Development in progress

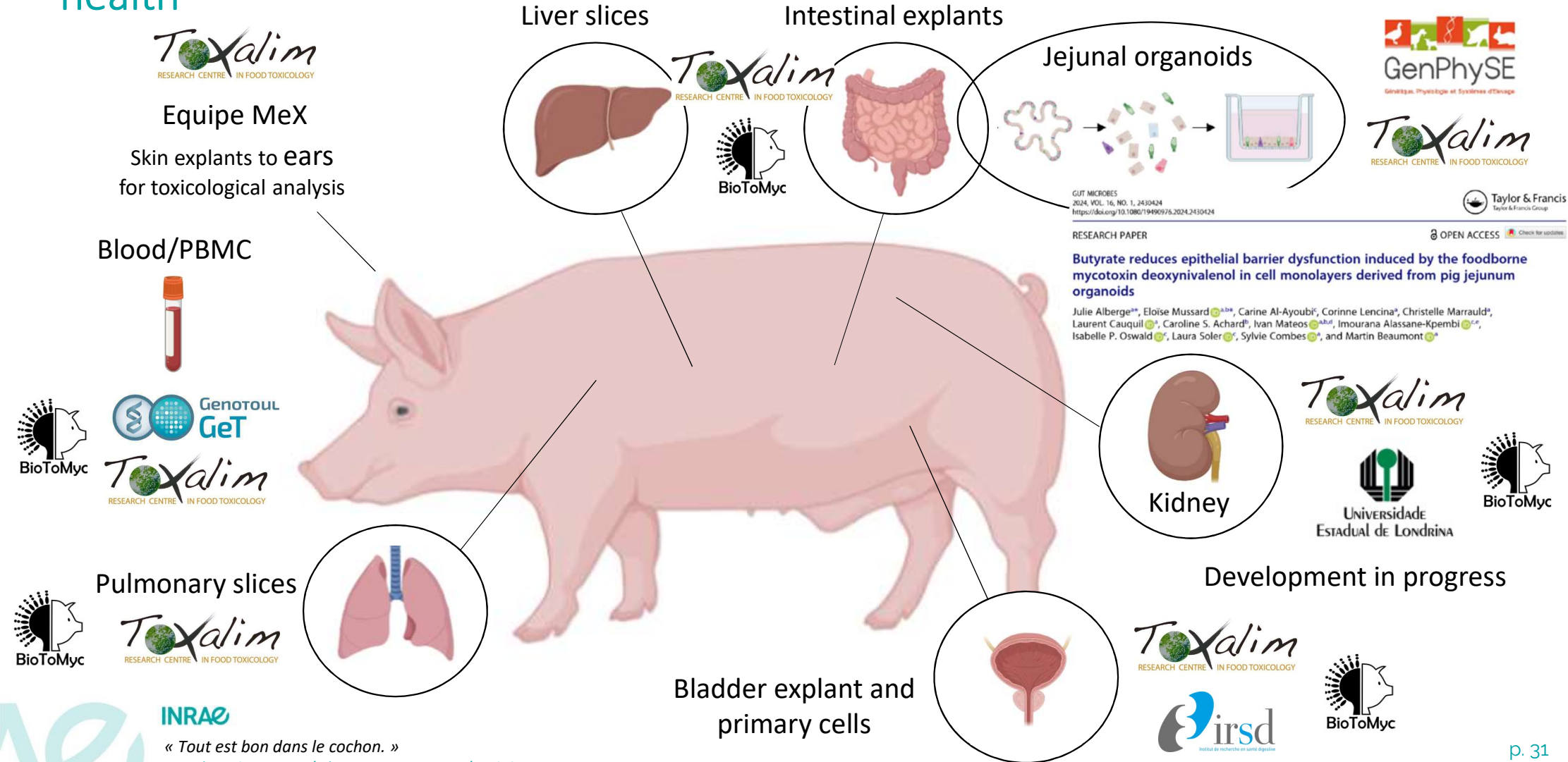


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Collaborations of the BioToMyc Team: alternative models to animal experimentation in pig



➤ Future research and development of the BioToMyc Team for animal and human health



> Acknowledgements



Intestinal explants

P. Pinton
I. Alassane Kpembé
A. Pierron
C. Al Ayoubi
D. Payros
G. Garcia
I. Oswald

Liver slices

P. Pinton
L. Soler
M. Garofalo
N. Le Moël
O. Labat
I. Oswald

Bladder explant and kidney slices

A. Durant PhD
D. Payros
P. Pinton
M. Penary
I. Oswald
J.P. Nougayrède

Zootecnie

M. Albin
E. Rousseau-Bacquié

Histomorphology

A.P. Bracarense

Ears

Sandrine Bruel
Elodie Person

Transcriptomic analysis

Y. Lippi
G. Payros
C. Naylies
S. Puel

Intestinal Organoids

M. Beaumont
J. Alberge

EZOP



GAEC de CALVIGNAC



« Tout est bon dans le cochon. »
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