Intestinal stem-cell organoids as experimental models to investigate feed efficiency

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WAGENINGEN UNIVERSITY & RESEARCH

100years 1918 — 2018

Animal Breeding & Genomics

Host-Microbe Interactomics

HMI

BREED4FOOD

Acknowledgement

Host-Microbe Interactomics

HMI

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Topigs Norsvin

Animal Breeding & Genomics

Animal nutrition

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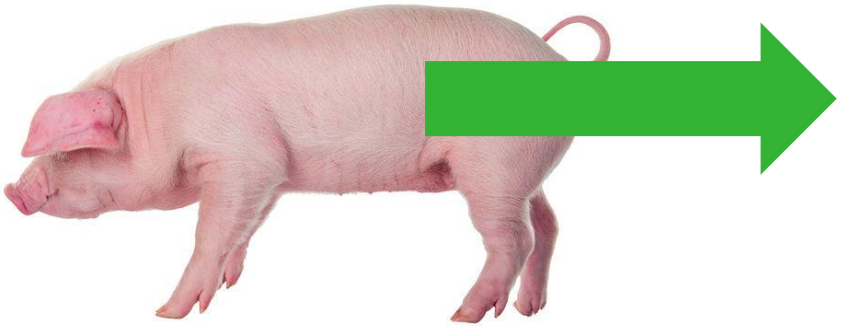
100years 1918 — 2018

Feed efficiency

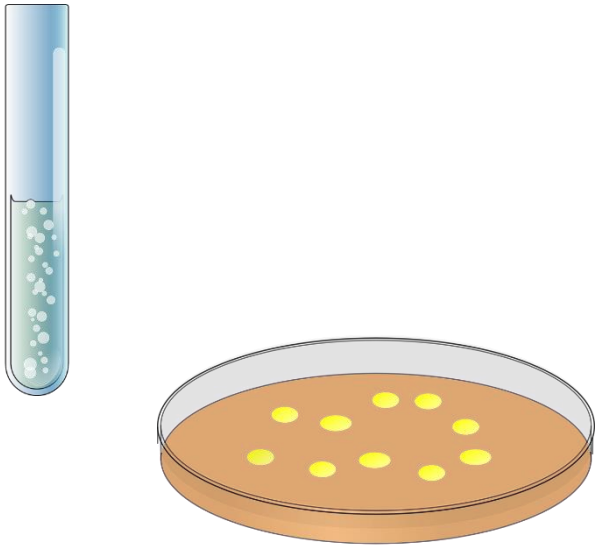
- Important trait
- Feed conversion ratio
- Biological mechanisms unclear & very complex

New technologies

- In vivo

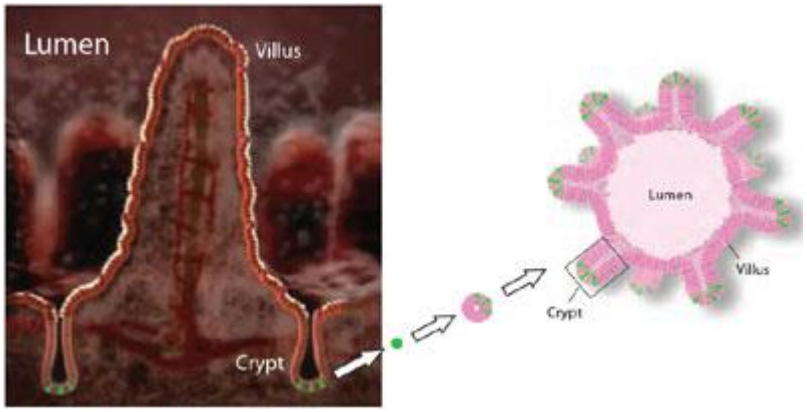


- In vitro



Organoids

- 3-D structure developed in vitro
- Contains major cell types of an organ
  - Similar spatial organization
  - Recapitulating specific function(s) of the organ
- Powerful experimental models



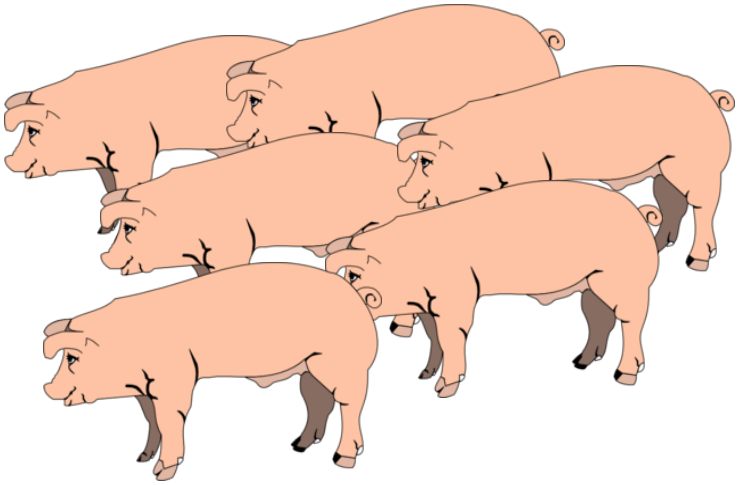
T. Sato and H. Clevers

Aim

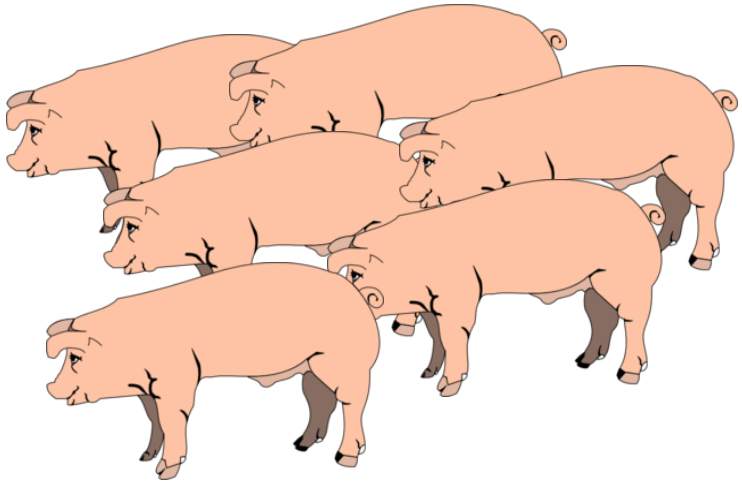
To show the potential of **organoids** as models to provide detailed **molecular** understanding of the underlying mechanisms of **feed efficiency**

Proof of principle to compare *in vitro* nutrient transport in ileal organoids to *in vivo* data on feed efficiency in pigs

Experimental design

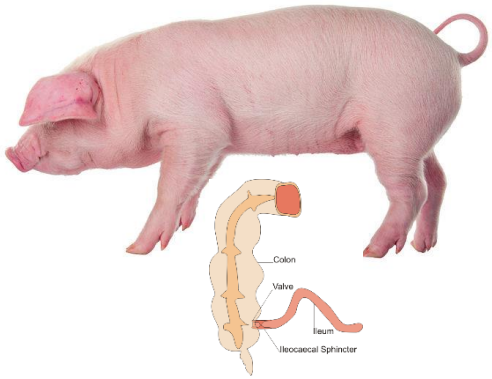


Efficient pigs (HIGH)
FCR = 2.19 ± 0.03



Less efficient pigs (LOW)
FCR = 2.61 ± 0.04

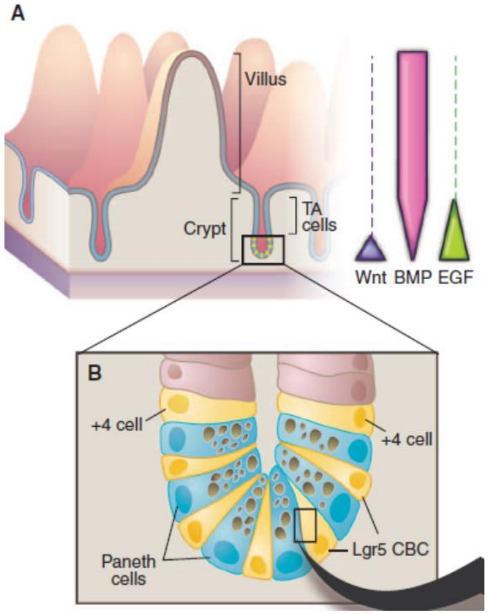
Tissue

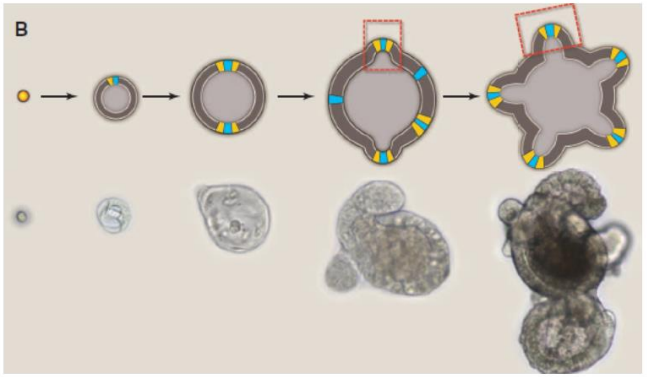


Ileum ~ 50 cm from ileo-caecal valve

Growing Self-Organizing Mini-Guts from a Single Intestinal Stem Cell: Mechanism and Applications

Toshiro Sato[1]* and Hans Clevers[2]*

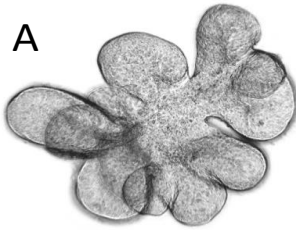




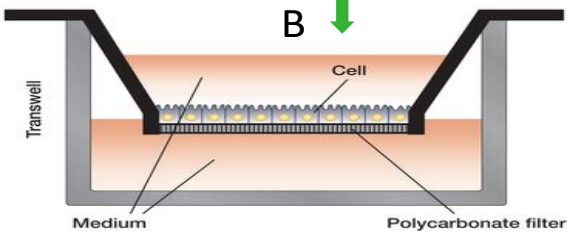
Organoid culture system

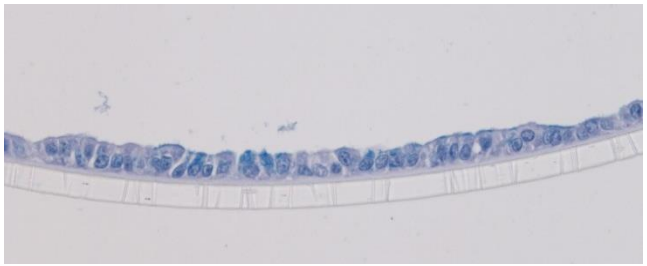
Nutrient or immune challenge
(e.g. e-coli, glucose)

A



B





3D organoids after ~10d culture in Matrigel

Form 2D epithelial monolayers using matrigel-coated Transwell membranes

Measure resistance or uptake

N = 4
LC/ mass-spectrometry

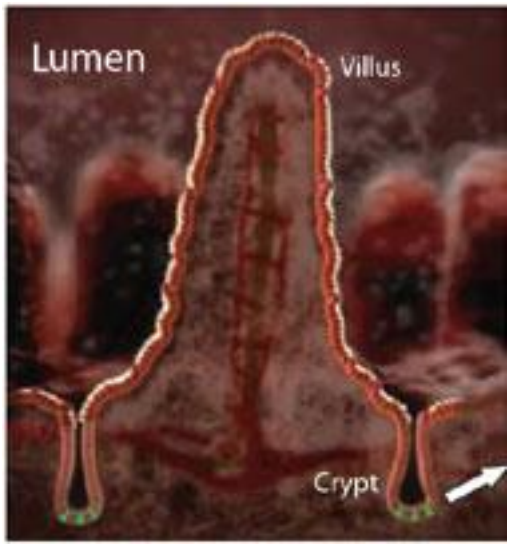
Van der Hee et al., 2018 Stem Cell Research; Figure J. Wells, HMI-WUR

Measurements

- Histology
- Resistance to commensal *E. coli*
- Transport study using glucose and amino acids
- Gene expression (RNA seq – molecular phenotypes)

Results – Histology

- Villus:crypt length
- Thickness wall
- Erosion of villi tips
- Granolucytes
- Infiltration lymphocytes
- Blunted villi



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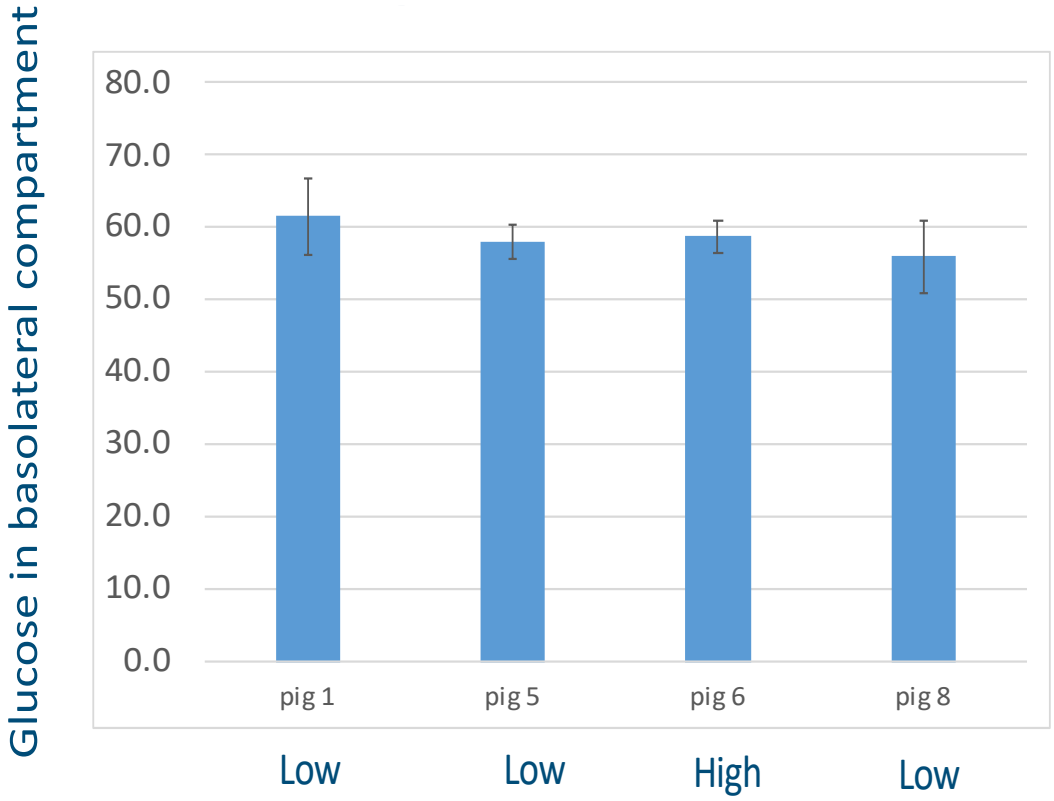
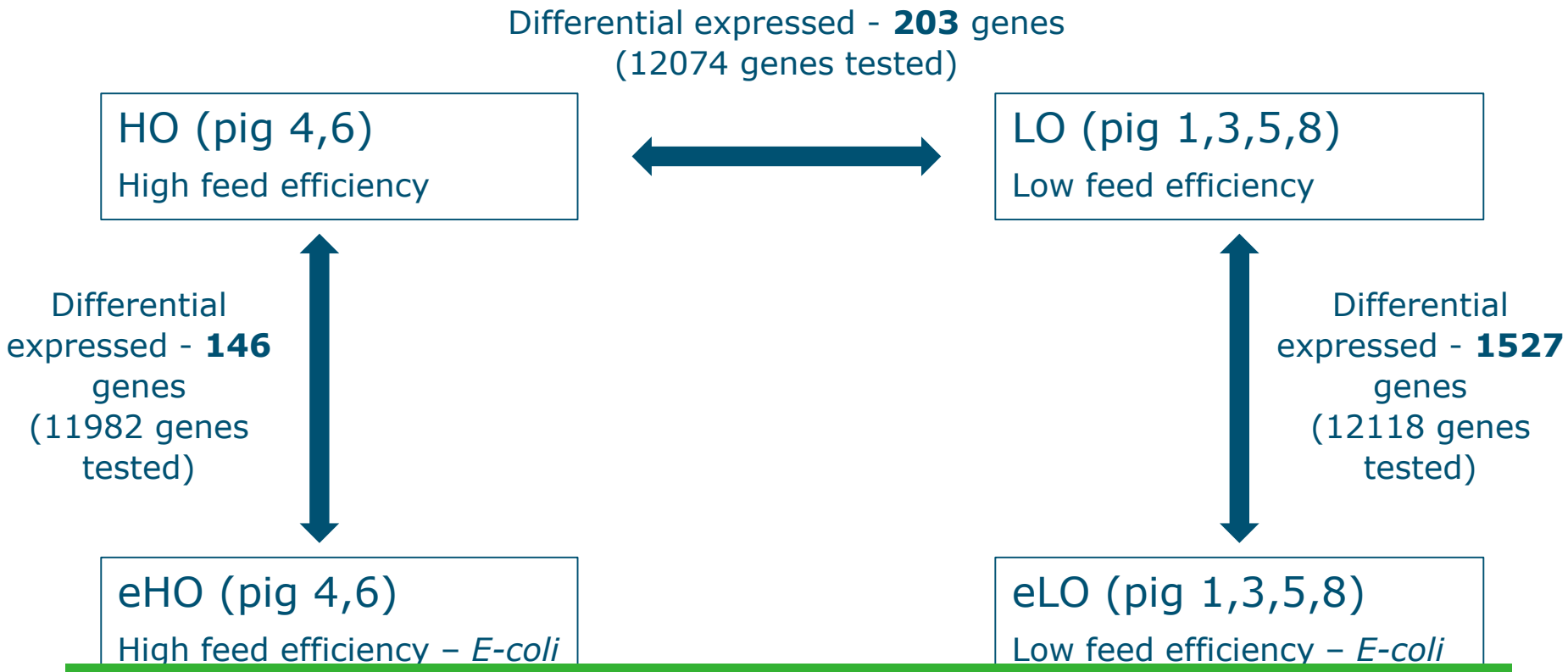
No clear differences in histology between efficient and less efficient pigs

Results – transport study



No differences in glucose transport between pigs

Results – gene expression



Indication: different number of genes expressed between HIGH and LOW and between challenged and unchallenged

Challenges

- Contamination of tissue
- Robust culture of organoids
- Validate the use of the organoids as proxy for *in vivo* performance
- High-throughput phenotyping of individual animals

Take home message

- New possibilities to understand the potential role of intestinal functions in feed efficiency
- Provide new phenotyping tools

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