ANIMAL STUDY EVIDENCE FOR THE POTENTIAL SAFETY AND EFFECTIVENESS OF AN ARTIFICIAL WOMB

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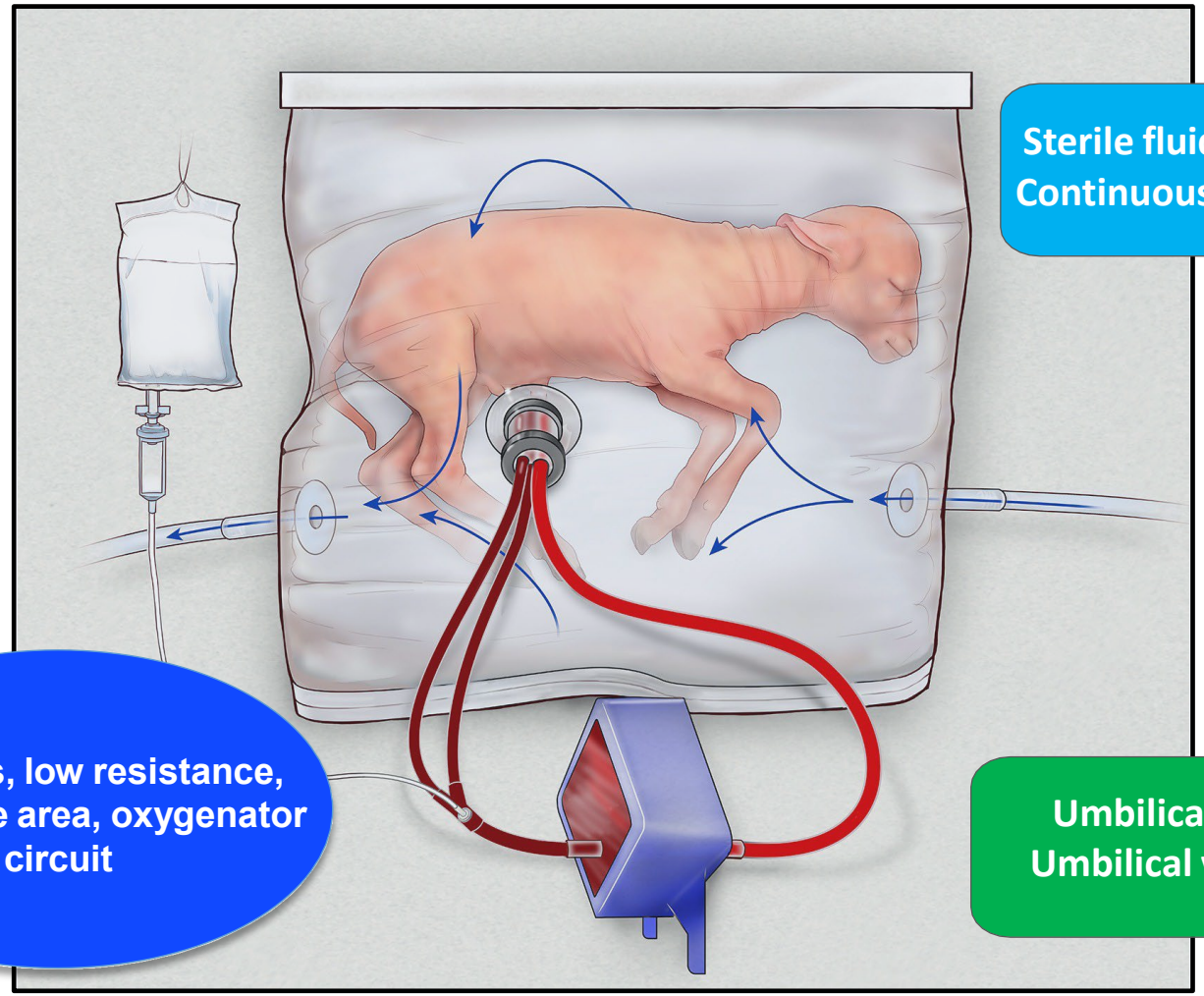
Rationale for an Artificial Womb:

This technology is designed to maintain normal fetal physiology and development by mimicking, as closely as possible, the environment of the maternal womb

By extending gestation, this technology is expected to **improve the survival and wellbeing** of premature neonates.

This technology allows a neonate to be **quickly transferred to the standard of care** if needed.

Essentials Components of the Artificial Womb



Sterile fluid environment,
Continuous fluid exchange

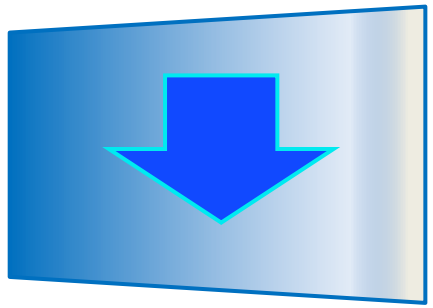
Pumpless, low resistance, low surface area, oxygenator circuit

Umbilical Artery (2)
Umbilical vein conduit

Essential Components and Role in the AW

Sterile fluid Environment, Continuous fluid exchange

- Sterile fluid environment
- **Allows liquid breathing/swallowing**
- Temperature
- Fluid balance
- Allows normal movement
- Prevents mechanical/pressure trauma



Morbidities of Extreme Prematurity

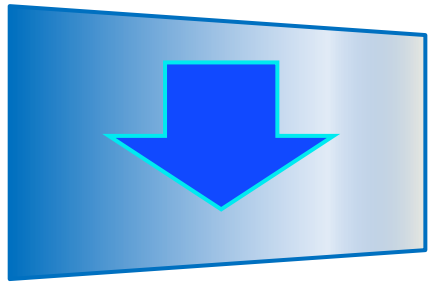
Ventilatory Failure
RDS/BPD
Neonatal Sepsis
NEC
Mechanical/pressure injury
Temperature instability
Fluid imbalance

Pumpless, low resistance, low surface area, oxygenator circuit

+

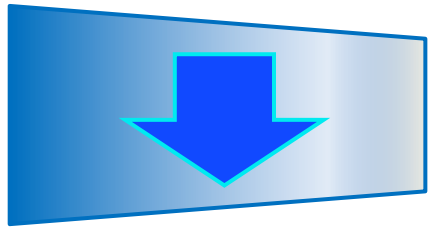
Umbilical Artery (2)/*Umbilical vein* conduit

- **Mimics placental circulation/maintains low cardiac workload**
- Allows autoregulation of circuit flow (UV/DV)
- **Allows high physiologic blood flow at physiologic pO_2 (normal O_2 delivery)**
- **Maintains the fetal circulation**



Circulatory instability
Cardiac failure
PDA related complications
IVH/NDI
ROP

- Access to circulation (no catheters)
- Minimizes surgical manipulation/erosion/ dislodgement
- Reduces need for narcotics/anxiolytics/ paralysis



Catheter complications
Sepsis
NDI

Animal Models – Why the Lamb?

Fetal Lamb model is physiologically well-defined and relevant to human fetal physiology and development.

Fetal lamb is large enough at developmentally relevant time points for surgical manipulation

Primate models (rhesus macaque and baboon) are too small (100 – 200 gms) at developmentally relevant timepoints.

The porcine model is size equivalent and has a similar umbilical cord structure but developmentally advanced (near term)

There is no perfect animal model!

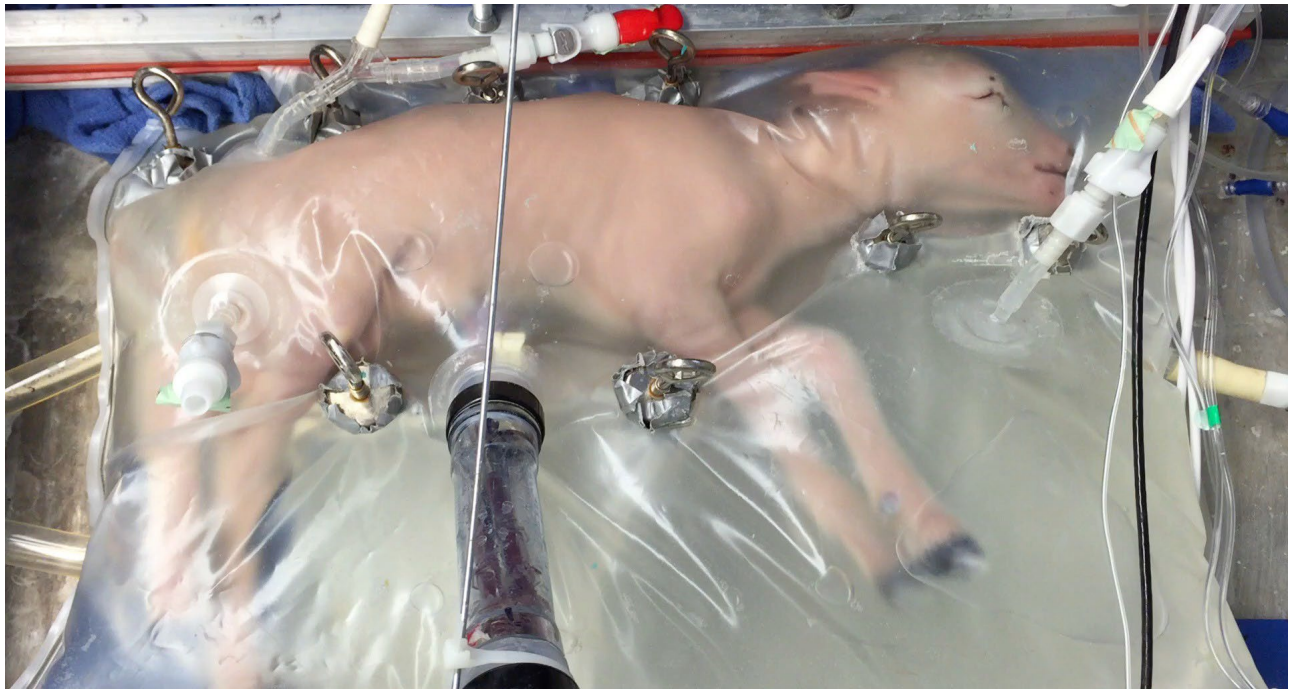
The technology can maintain fetal physiology and support normal growth and organ development*

Fetal Lambs supported for 25-28 days

With **normal**:

- **Fetal** circulation
- Cardiovascular parameters
- Cardiac function
- Oxygen delivery
- Somatic growth
- Metabolism
- Lung development
- Brain development
- Gut development

105-113-day GA Lamb Model Developmentally Equivalent (Lung) To 23-25-week GA Human Neonate*



nature COMMUNICATIONS

ARTICLE

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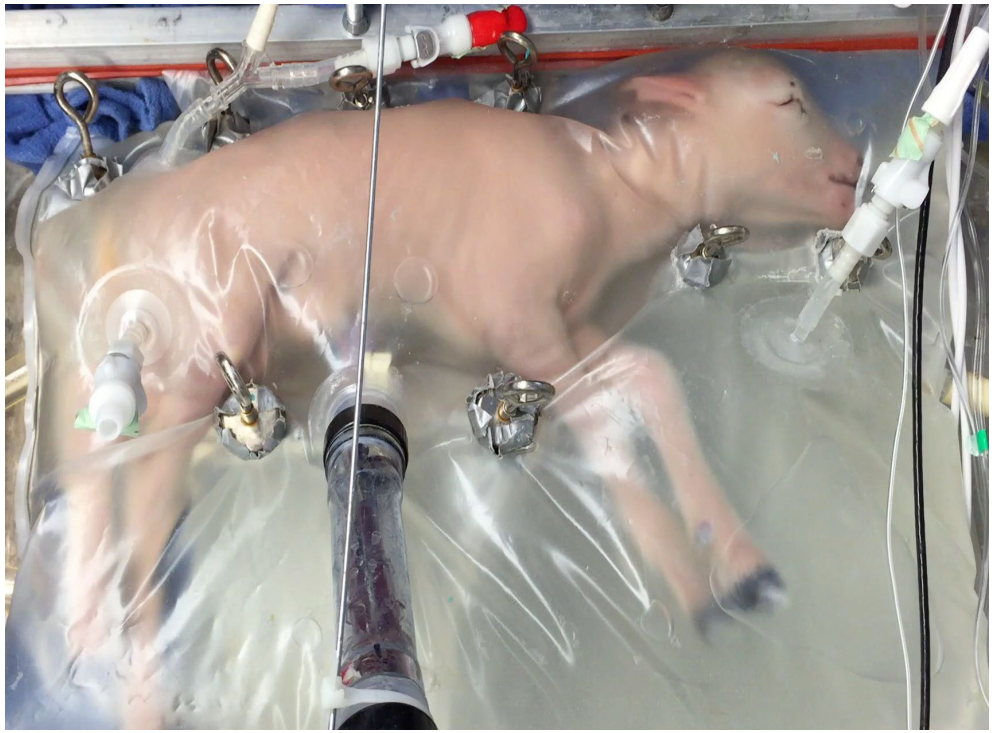
An extra-uterine system to physiologically support the extreme premature lamb

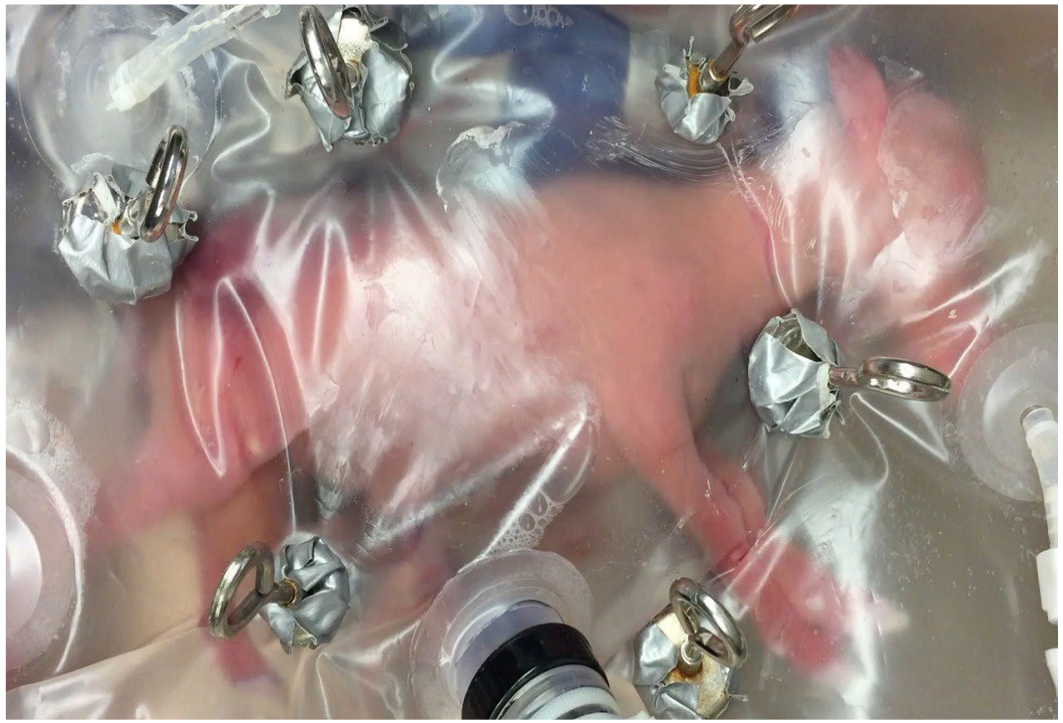
+ Additional studies

Human Equivalency: Pulmonary and Neurodevelopmental Ovine Models

GA Lamb Model	105 – 113 day	90-95 day
Weight	1.3-1.8 kg	0.6-1.1 kg
Lung	Canalicular Stage (Human 23-25-week equivalent)	Pseudoglandular-canalicular transition (human 17-19 wks)
Germinal Matrix	Mature, Medullation near complete	Immature, Medullation early stage (human 23-25 wks)

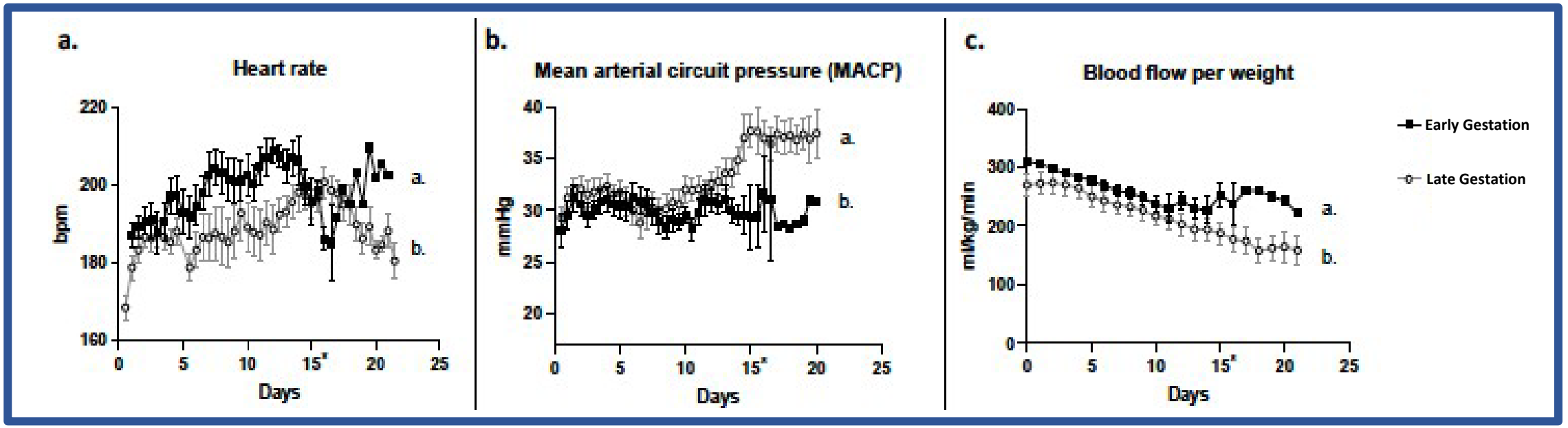
Note: Data presented in the following 5 slides include data published in Nature Comms (2017) and the pending publication in Pediatric Research including IUGR and mid gestation lamb data.





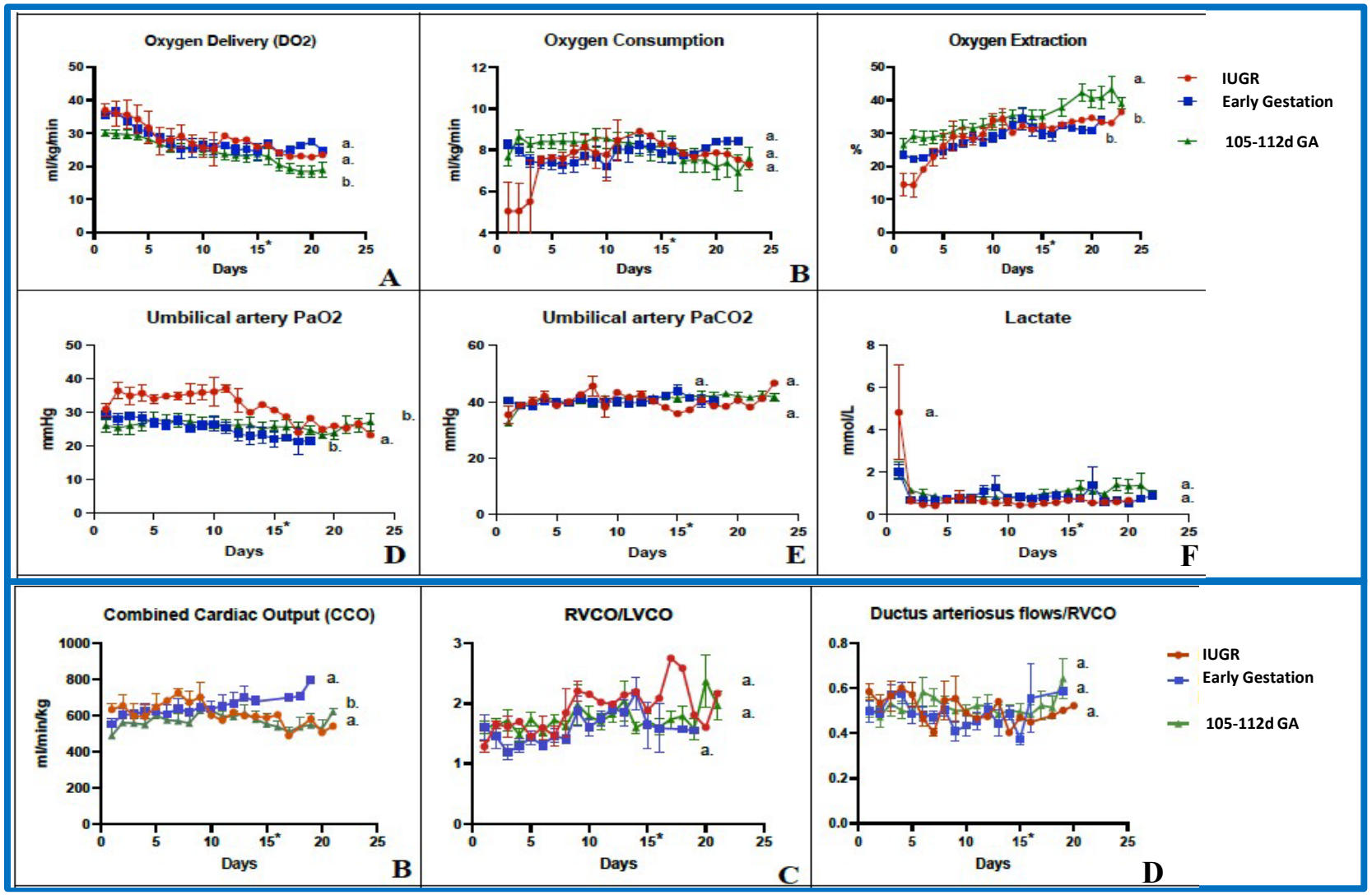
Findings	Late Gestation Model: lung development equivalent, evaluated all major organs, MRI and Histopathology	Mid-gestation Model: cardiovascular and neurodevelopmental equivalent, evaluated all major organs, MRI and Histopath

Physiologic Circuit Flow and Stable Hemodynamics



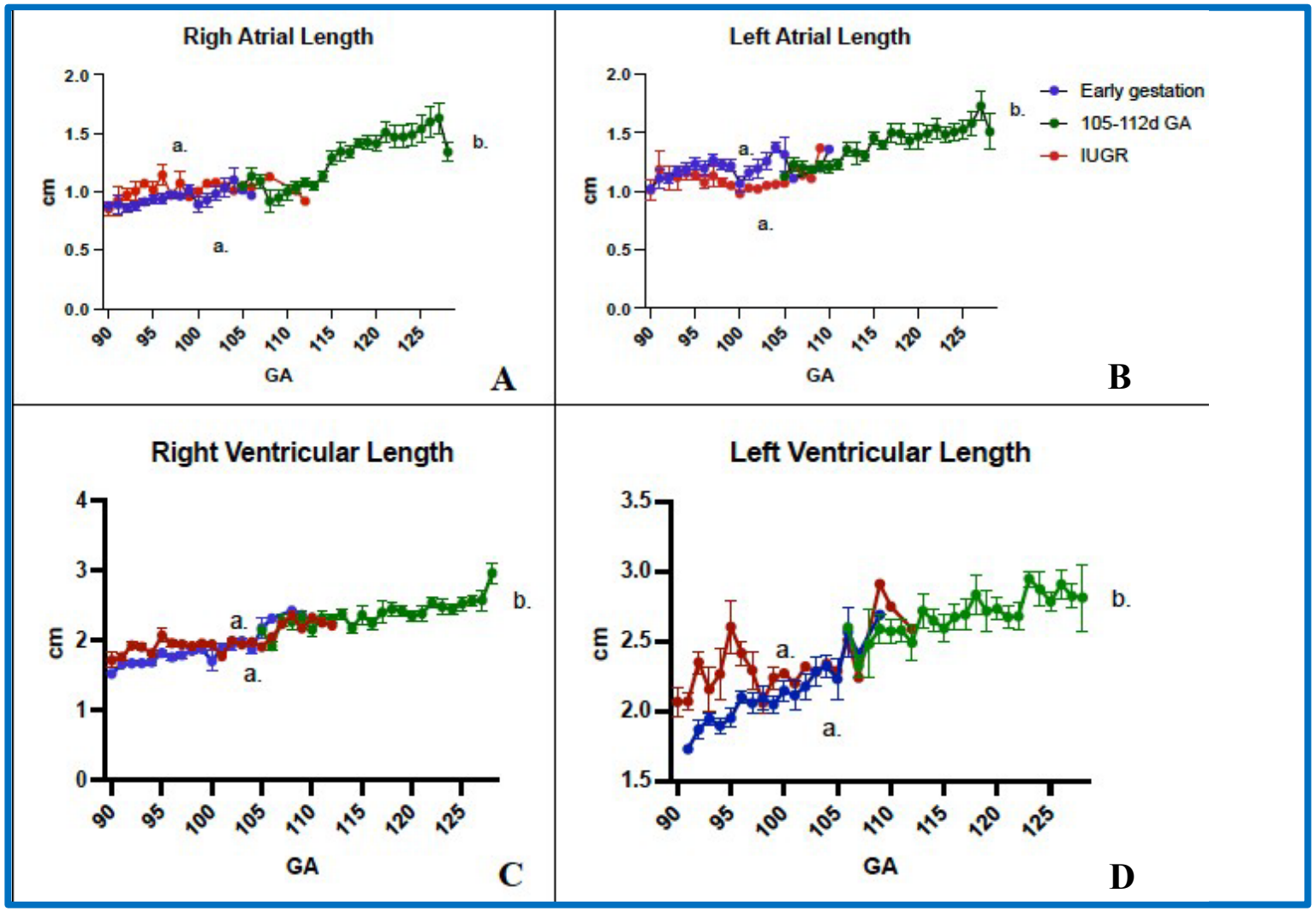
The Mid Gestation lambs, 90–95-day GA lamb model, maintain physiologic circuit flow and stable hemodynamics with circuit flow restriction for 14-21 days

Maintains Stable Oxygenation and Cardiovascular Parameters



Mid Gestation, 90–95-day GA lamb model, maintains stable oxygenation and cardiovascular parameters with circuit flow restriction for 14-23 days

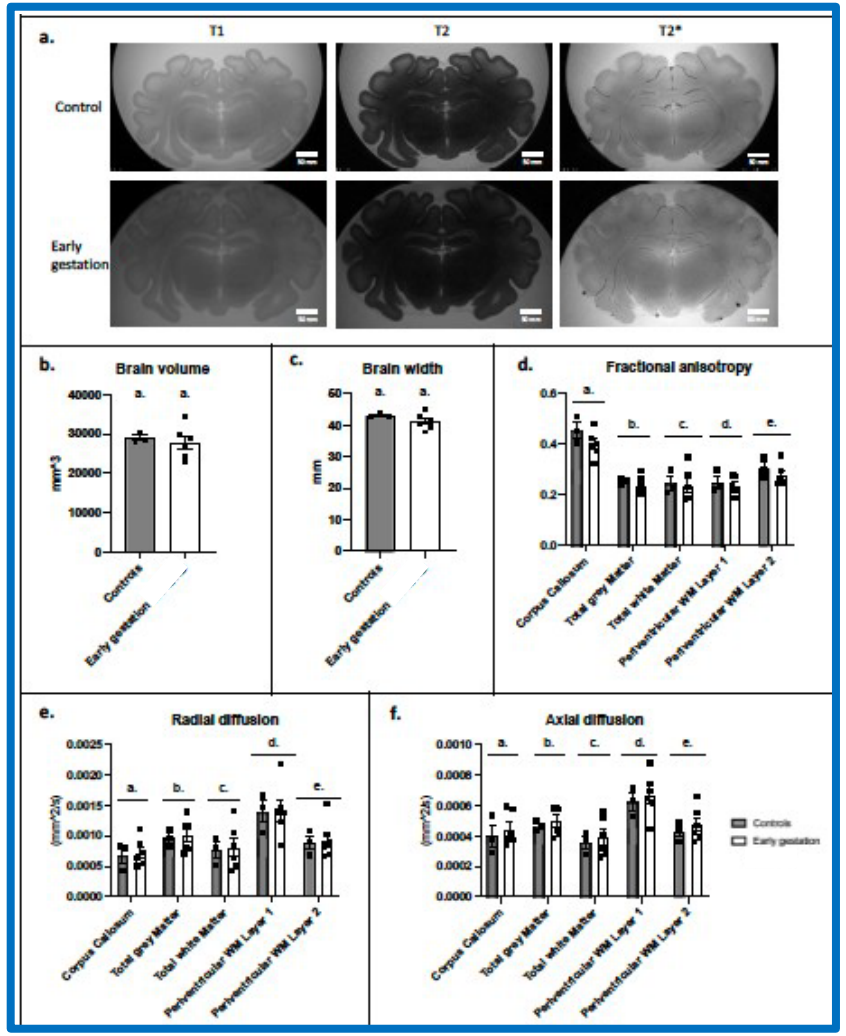
Cardiac Growth



Cardiac development: Spanning 90 – 130 days GA in the system

By all echocardiographic criteria, cardiac function, chamber size, and growth are normal in the artificial womb model

Brain Growth and Maturation – Cerebral MRI Findings



90-95 d GA Lamb Model

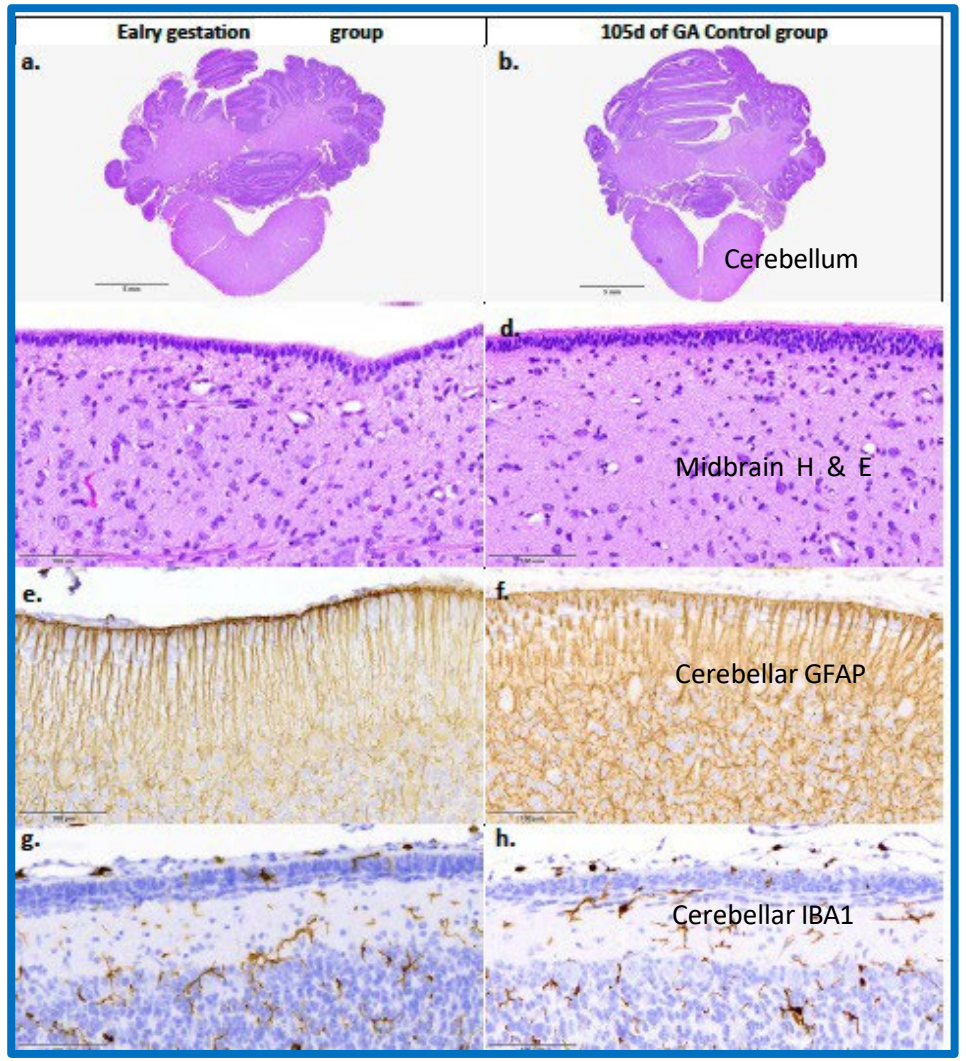
Assessed by an independent veterinary radiology consultant

Normal absolute volume and size of the brain relative to age matched controls

Normal maturation of all regions relative To age matched controls

No evidence of intra-ventricular hemorrhage or ischemic injury

Brain Growth and Maturation – Histology



90-95 d GA Lamb Model

Normal Cortical and Cerebellar Cortical Histology

Normal GFAP and IBA-1 staining

Normal cortical histology and medullation: Axonal sheath development and myelination of radiating cerebrocortical white matter tracts

Normal brain growth and development without evidence of IVH or ischemic injury in a developmentally relevant model

Evidence for Safety

The animal model studied is **robust and stable**. It has now been applied to over 300 lambs. One trained fellow/technician can care for three animals.

No observed acute irreversible events that threaten survival or neurologic injury (e.g., irreversible cord spasm, circuit thrombosis, cannula erosion/dislodgement, major hemorrhage including IVH, and/or organ failure).

One connection to the fetus with the umbilical cannulas – this allows **rapid conversion to standard of care at any time during the therapy if O_2 delivery is threatened**. This is a major safety feature of the technology.

Evidence for Potential Clinical Benefit

Avoidance of the premature transition from the **fetal** to postnatal circulation (maintenance of the **fetal** circulation, hemodynamic stability)
Avoidance of exposure to mechanical, temperature, and septic stress (aseptic fluid environment)
Avoidance of the premature requirement for gas ventilation (maintenance of normal **fetal** breathing and fluid filled lungs)
Avoidance of intracorporeal catheters, tubes, narcotics.

Potential to prevent/reduce death and the major morbidities of prematurity

BPD

IVH

NEC

ROP

Sepsis

Neurodevelopmental impairment

Artificial Womb:

Maintains normal Fetal Physiology

E. A. Partridge et al. / Nature Communications Article (2017)
P.E. McGovern et al. / Journal of Pediatric Surgery 55 (2020) 2115–2123 (late gestation lambs)
A. Dave et al. / Scientific Forum Abstracts Vol 235, No 5S-1, Nov Sup 2022 (mid gestation lambs)

Supports normal organ development

P.E. McGovern et al. / Journal of Pediatric Surgery 55 (2020) 2115–2123 (late gestation lambs)
A. Dave et al. / Scientific Forum Abstracts Vol 235, No 5S-1, Nov Supp 2022 (mid gestation lambs)

Developed data that may support feasibility and safety for consideration of a clinical study

E. A. Partridge et al. / Nature Communications Article (2017)
P.E. McGovern et al. / Journal of Pediatric Surgery 55 (2020) 2115–2123 (late gestation lambs)
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