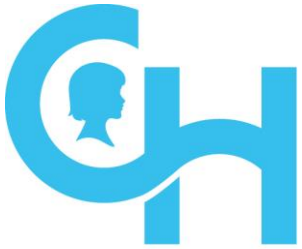
Creating the Artificial Womb

Marcus Davey, PhD

Disclosures

- No financial disclosures
- Patent holder on technology to be presented



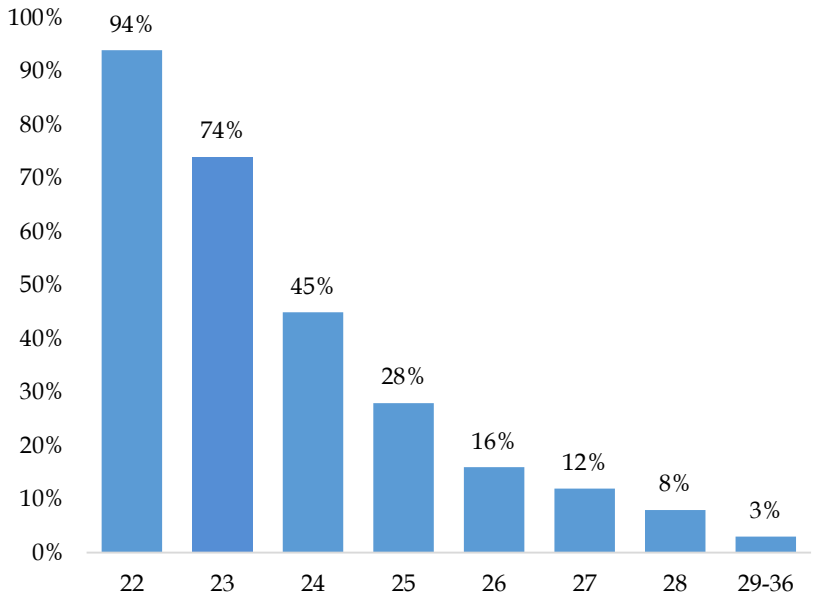
Children's Hospital of Philadelphia℠

A beginning, is a very delicate time

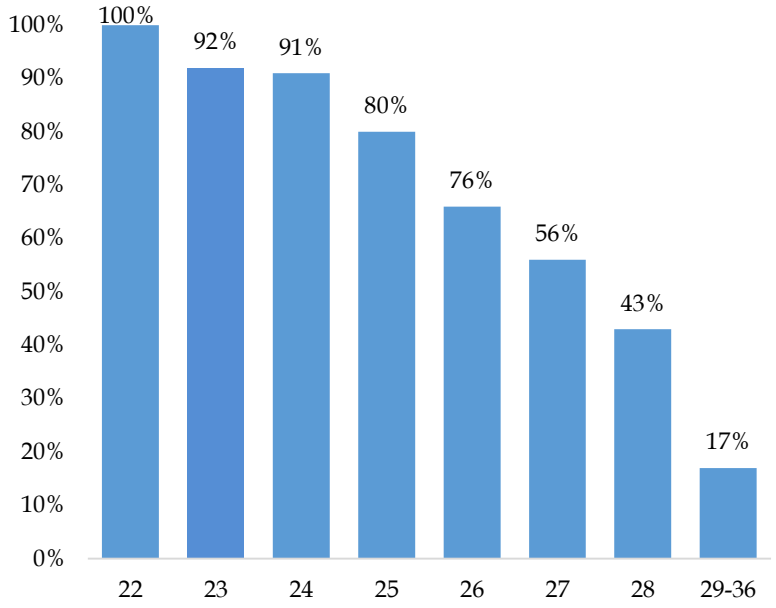
The lungs are the only major organ that have not performed their primary function before birth (Harding and Hooper)

Consequences of extreme prematurity (<28 wks)

Mortality



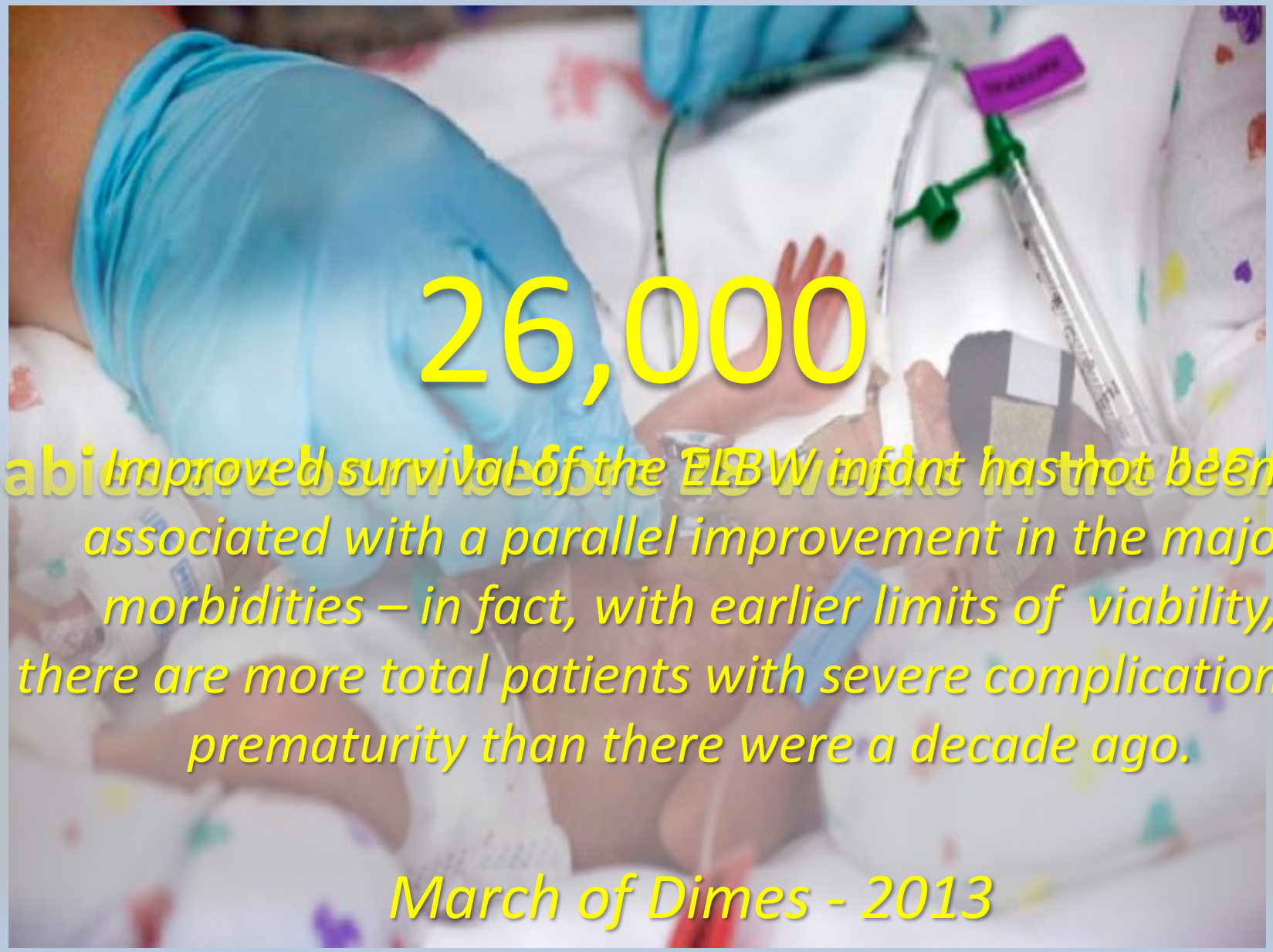
Morbidity



Organ immaturity and iatrogenic injury

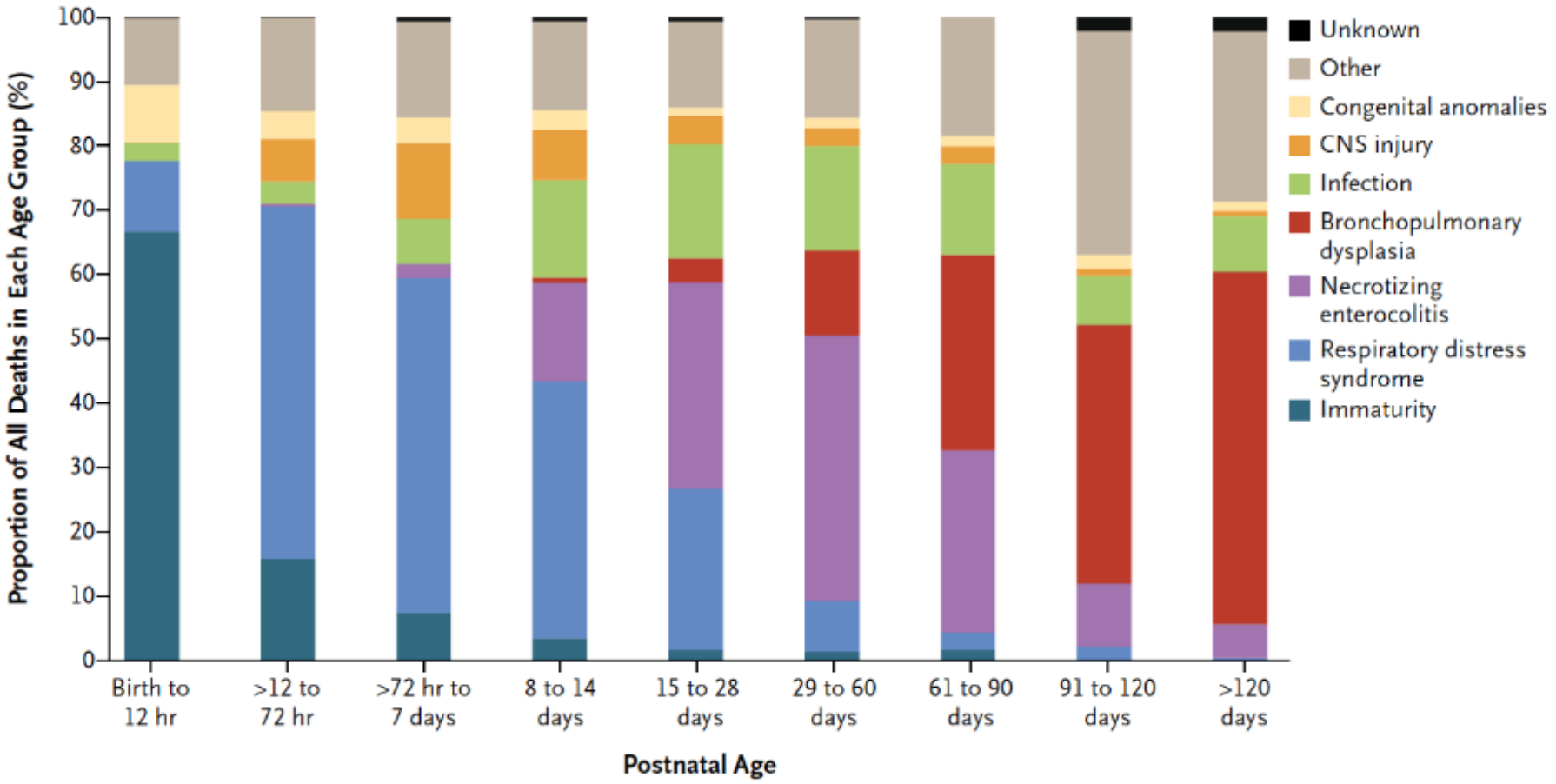
Nothing has changed over the past 15 years !

Consuming more medical resources ($32B in 2017)


26,000
Babies are born before 26 weeks in the USA.
Improved survival of the ELBW infant has not been
associated with a parallel improvement in the major
morbidities – in fact, with earlier limits of viability,
there are more total patients with severe complications of
prematurity than there were a decade ago.
March of Dimes - 2013

Extreme Prematurity – early mortality

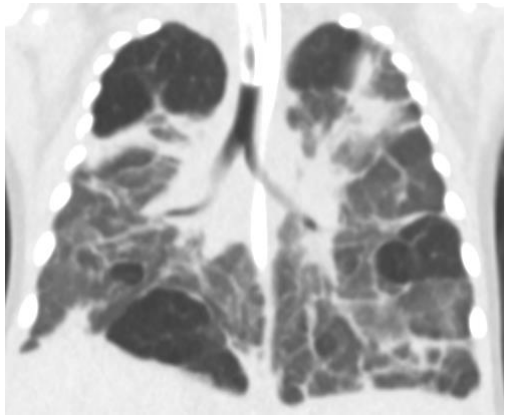
(Patel et al., *NEJM*, 2015)



Organ immaturity and iatrogenic lung injury are responsible for the majority of deaths

Any form of mechanical ventilation is **NON PHYSIOLOGIC**

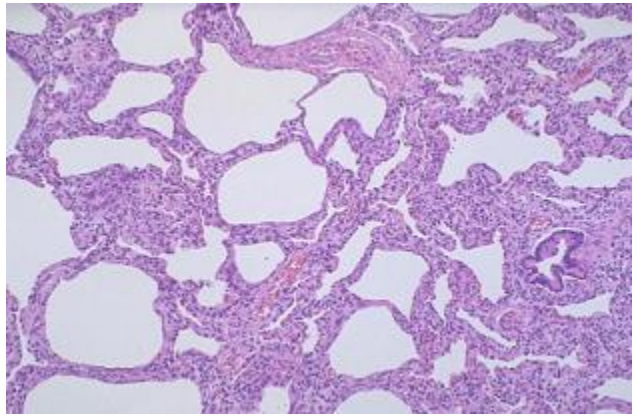
Mechanical ventilation, high FiO_2



Lung injury / arrested alveolar development

nCPAP, nIPPC, HHFNC, permissive hypercapnia AC/SIMV, VTV, HFJV, HFOV, synchronized NIPPV, non-Synchronized NIPPV, BiPAP, early iNO, Non-invasive iNO, steroids

No ventilation modality when studied by RCT has reduced death or BPD in extreme premature infants



We need better tools !

An artificial womb provides physiologic equipoise

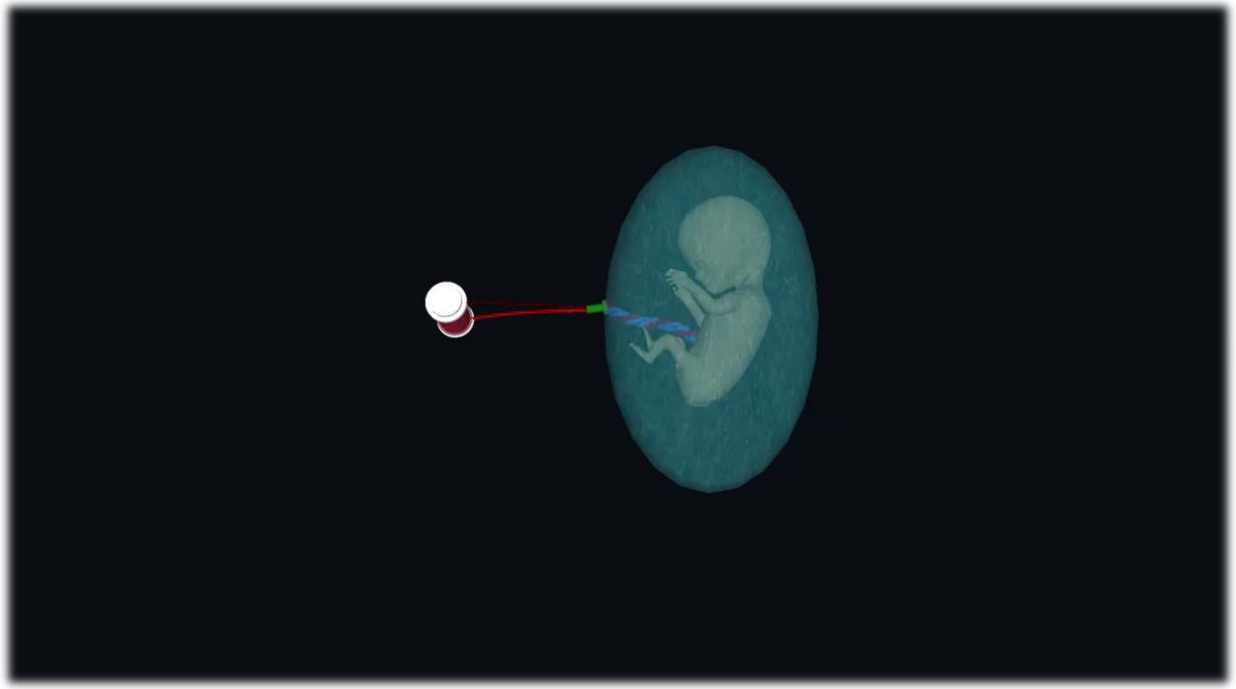
- Maintain the extreme preterm infant in a fetal-like environment to allow normal ongoing growth and maturation

- Avoid negative consequences of invasive respiratory support

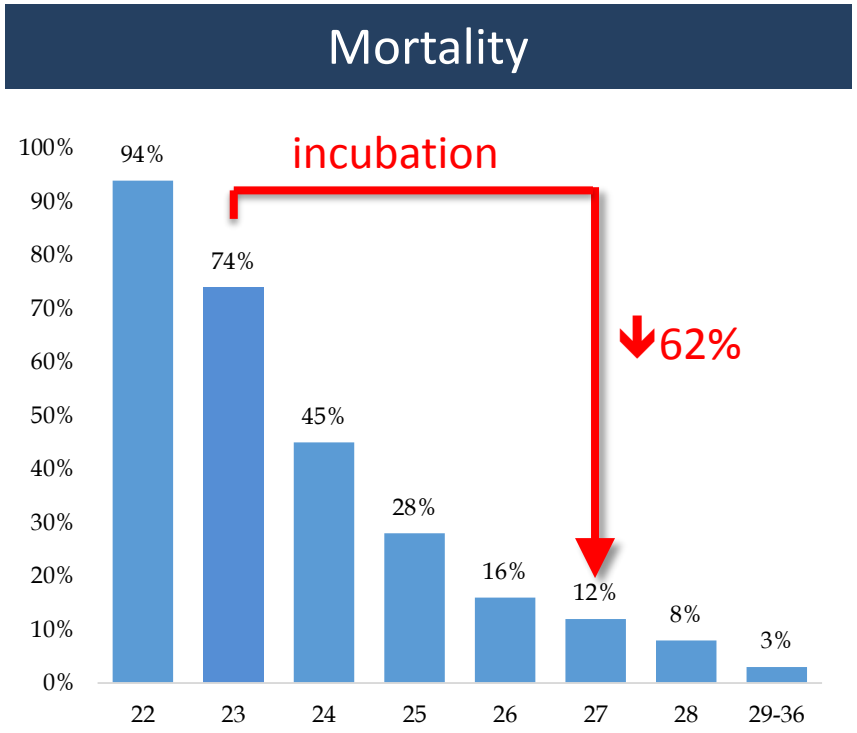
Membrane oxygenator
- ”pumpless” circuit

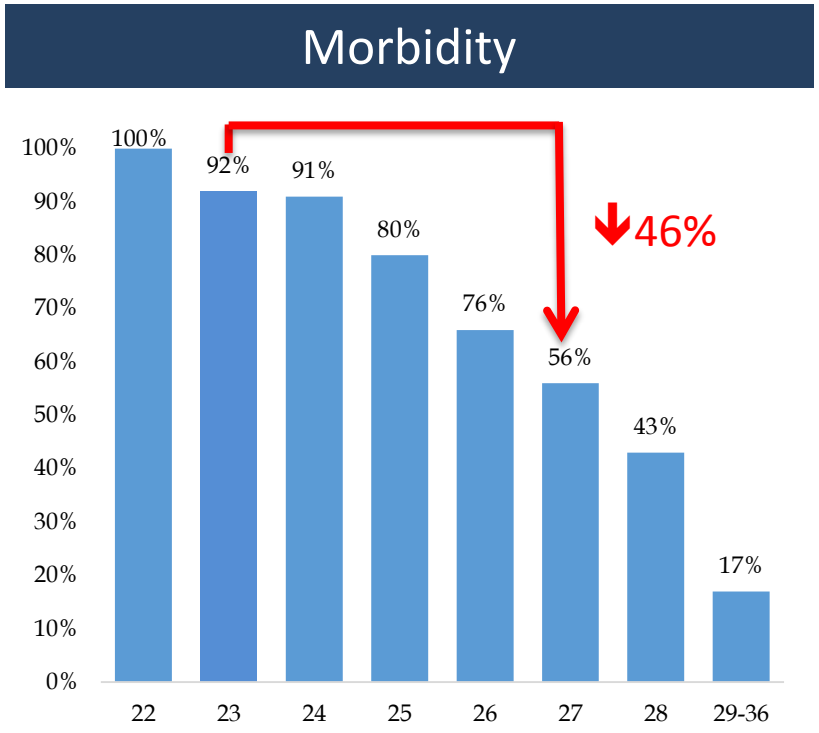
Umbilical cannulation
- native cord

Fluidic environment
-sealed /sterile



A NICU therapy to achieve a mortality and morbidity "time-shift"

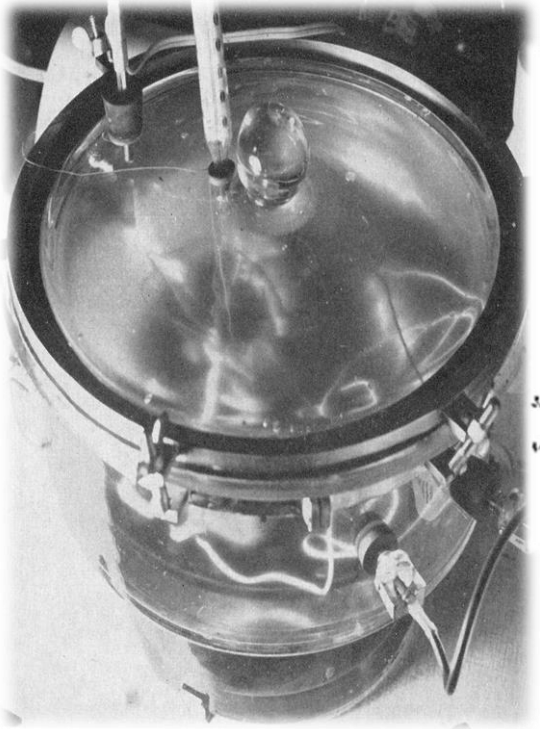


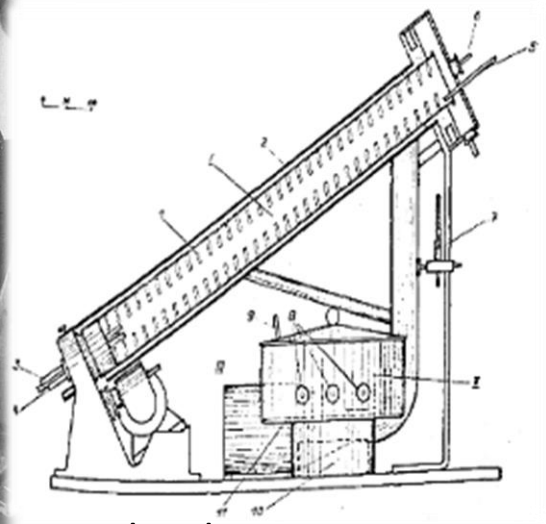


- Initial target population : 23-25 weeks
- Incubation period 3-4 weeks ➔ standard NICU care

History of the “Artificial Womb”

60 years of experimental effort



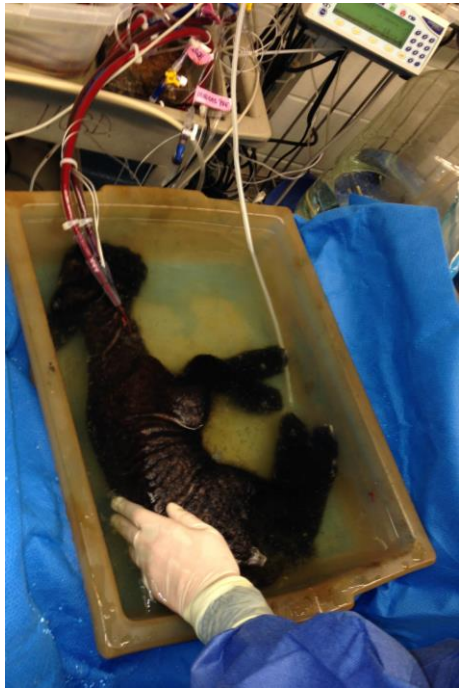


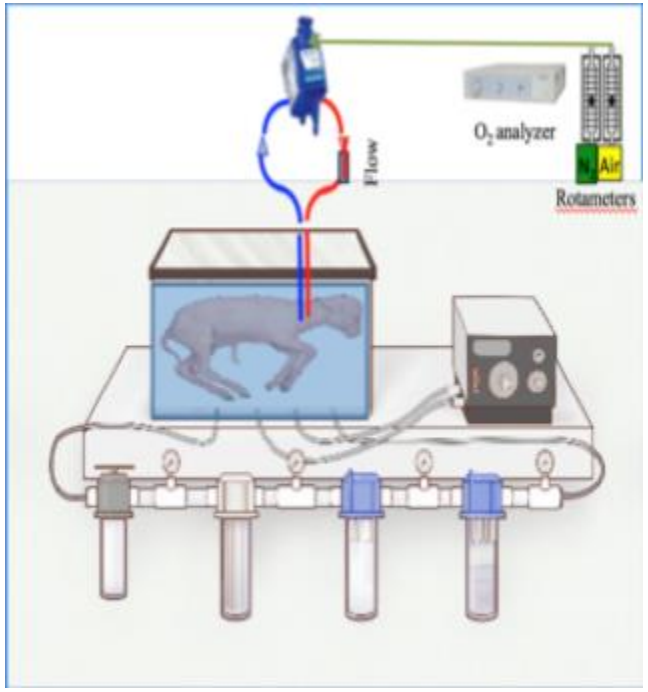
Blood oxygenator

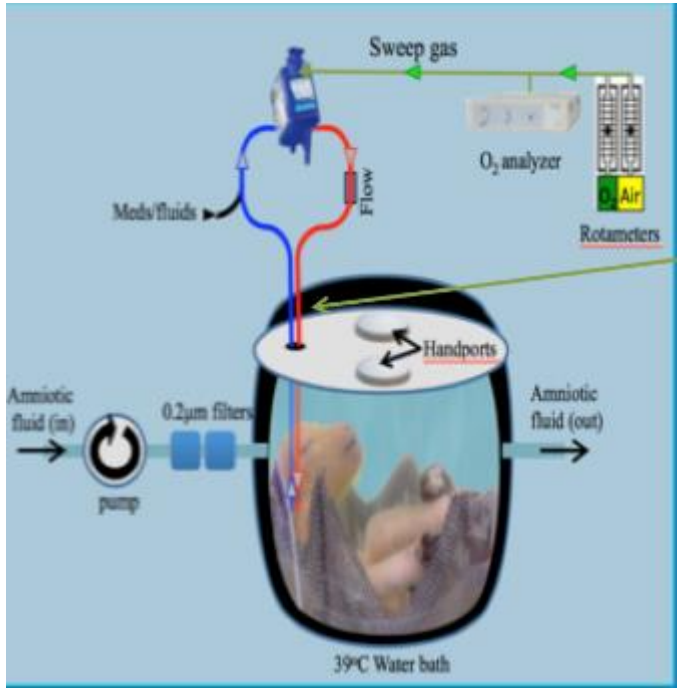
Obstacles

- Fetal heart extremely sensitive to pre-load or afterload imbalance
  - high resistance oxygenators, pumped circuits
- Infection is a major hurdle for warm fluidic environments
- UA/UV access is challenging due to spasm, vascular integrity

Evolution of the Artificial Womb (2013 -15)





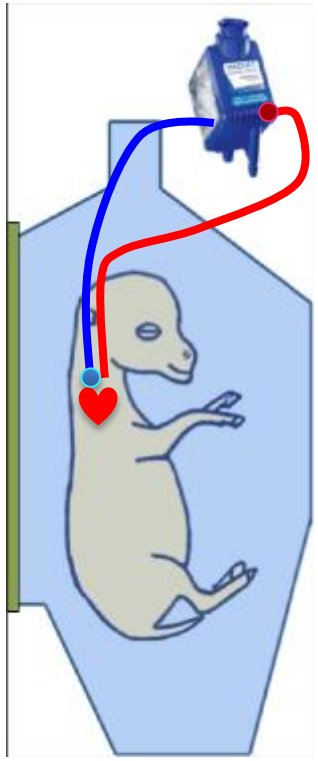


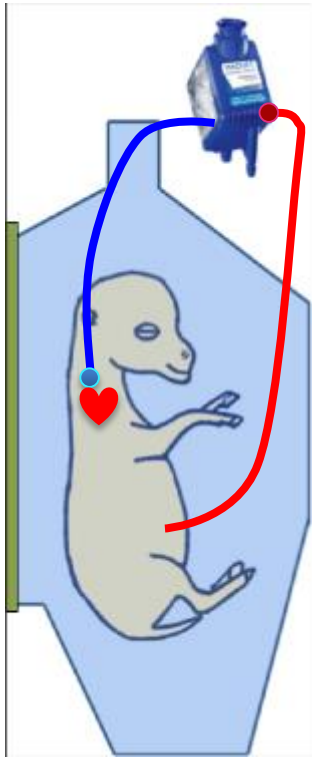
- Sepsis drove new design
- Switch from recirculation to circulation of synthetic amniotic fluid
- Duration of studies progressed from days to weeks

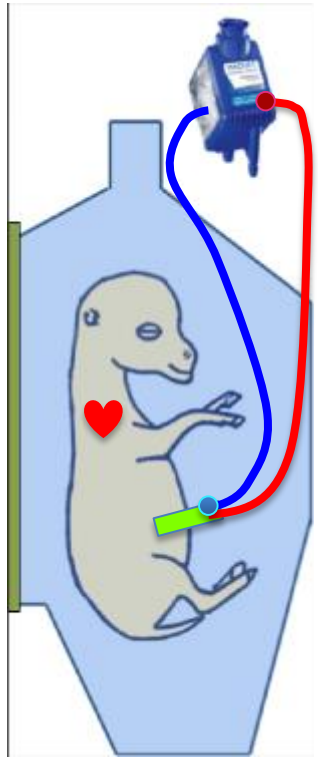
The CHOP Biobag

- Open sided design, adjustable size
- Adjustable number, size, and configuration of ports
- Silver impregnated polyethylene film
- Once sealed, completely closed system, efficiencies of flow and volume
- Translucent and sonolucent

Location, location, location



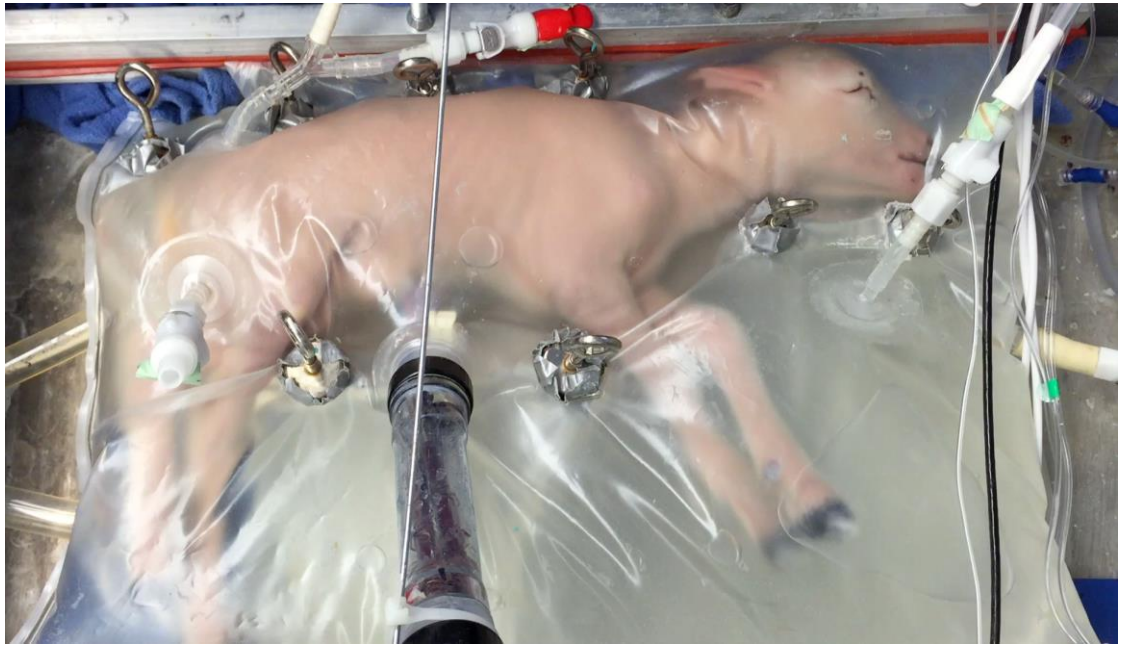




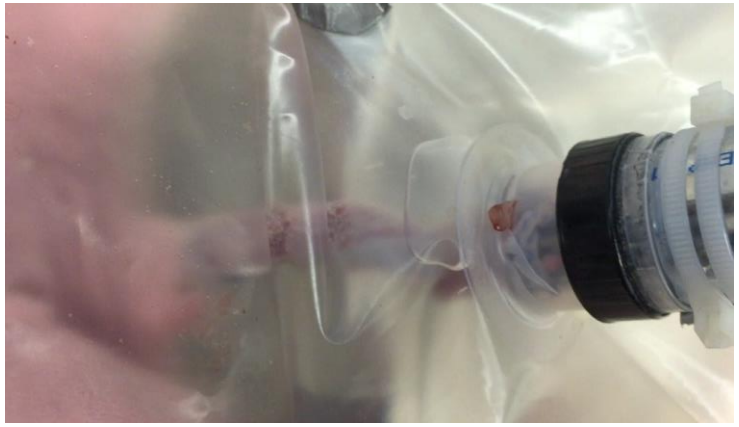
Cannulation site	Carotid-Jugular	Carotid - UV	UA(x2) – UV
Blood Flow (%norm)	45 %	80 %	100 %
O_2 delivery (%norm)	30 %	75%	100%
Flow interruptions /day	89	41	2
Problems	Hydrops ↑RH press.	↑risk of decannulation	

Umbilical cannulation of preterm lambs

EXTrauterine Environment for Neonatal Development- EXTEND



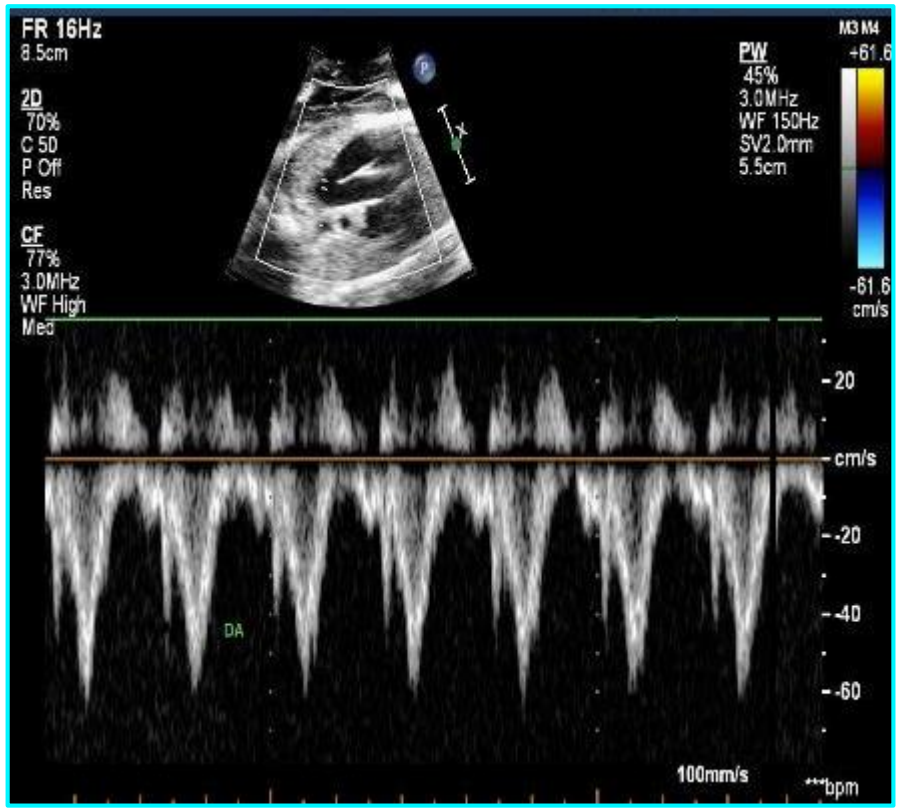
Umbilical interface

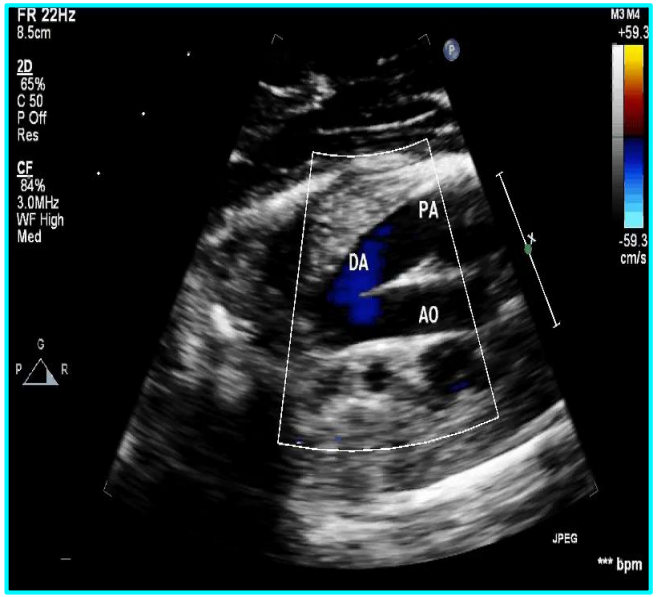


- up to 4 weeks of physiologic support
- continuous AF circulation
- no sedation – allows FBM's & swallowing
- normal CCO, O_2 delivery/consumption, CBF

Maintenance of the Fetal Circulation

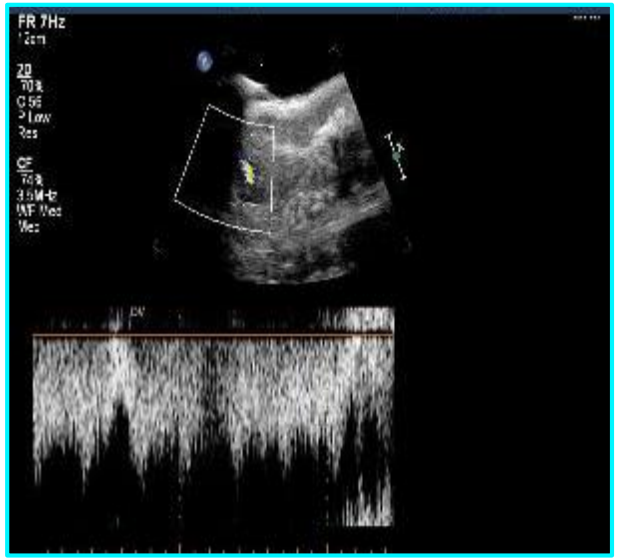
Ductus Arteriosus

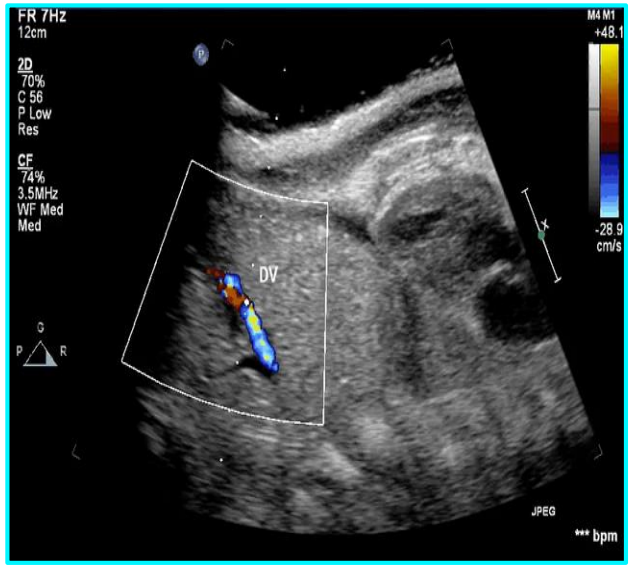




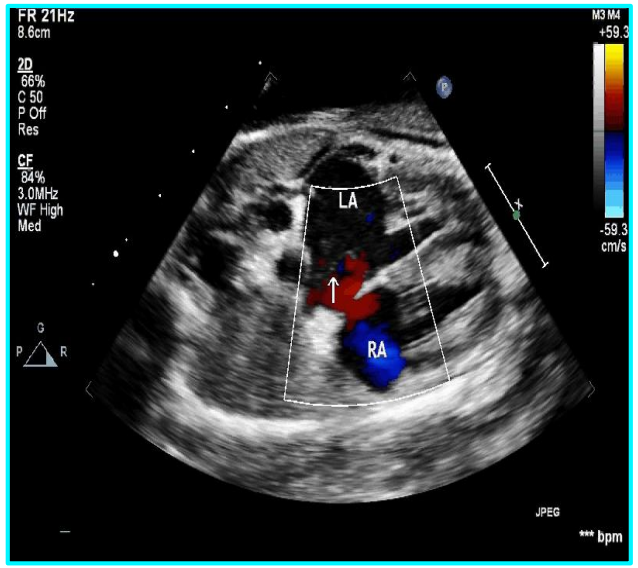
Maintenance of the Fetal Circulation

Ductus Venosus



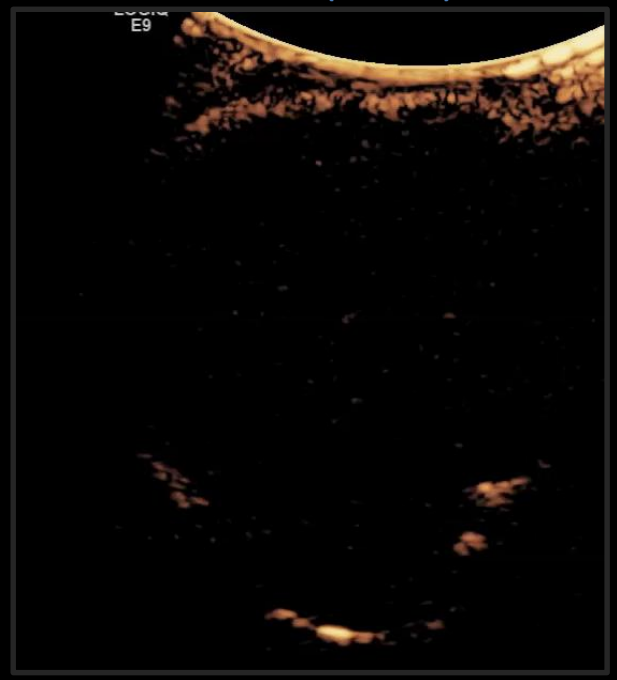


Foramen Ovale

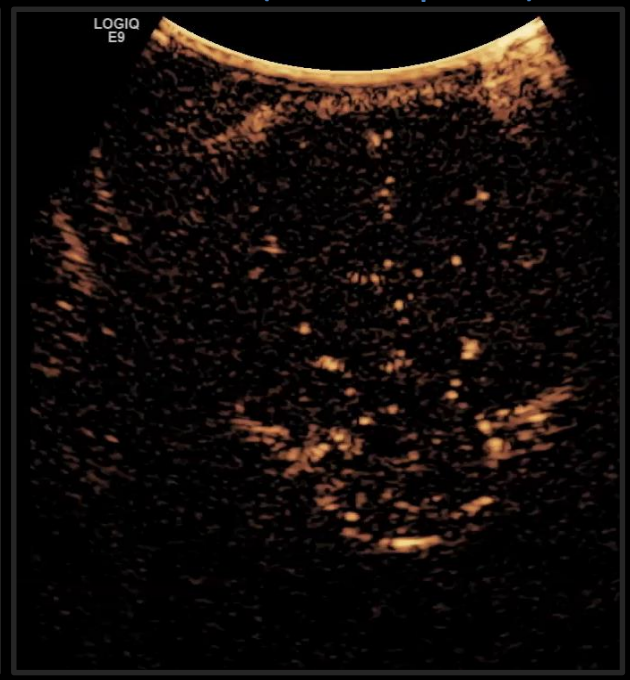


Contrast-enhanced ultrasound

Coronal (bolus)



Coronal (flash capture)



Saggital (HiRes)

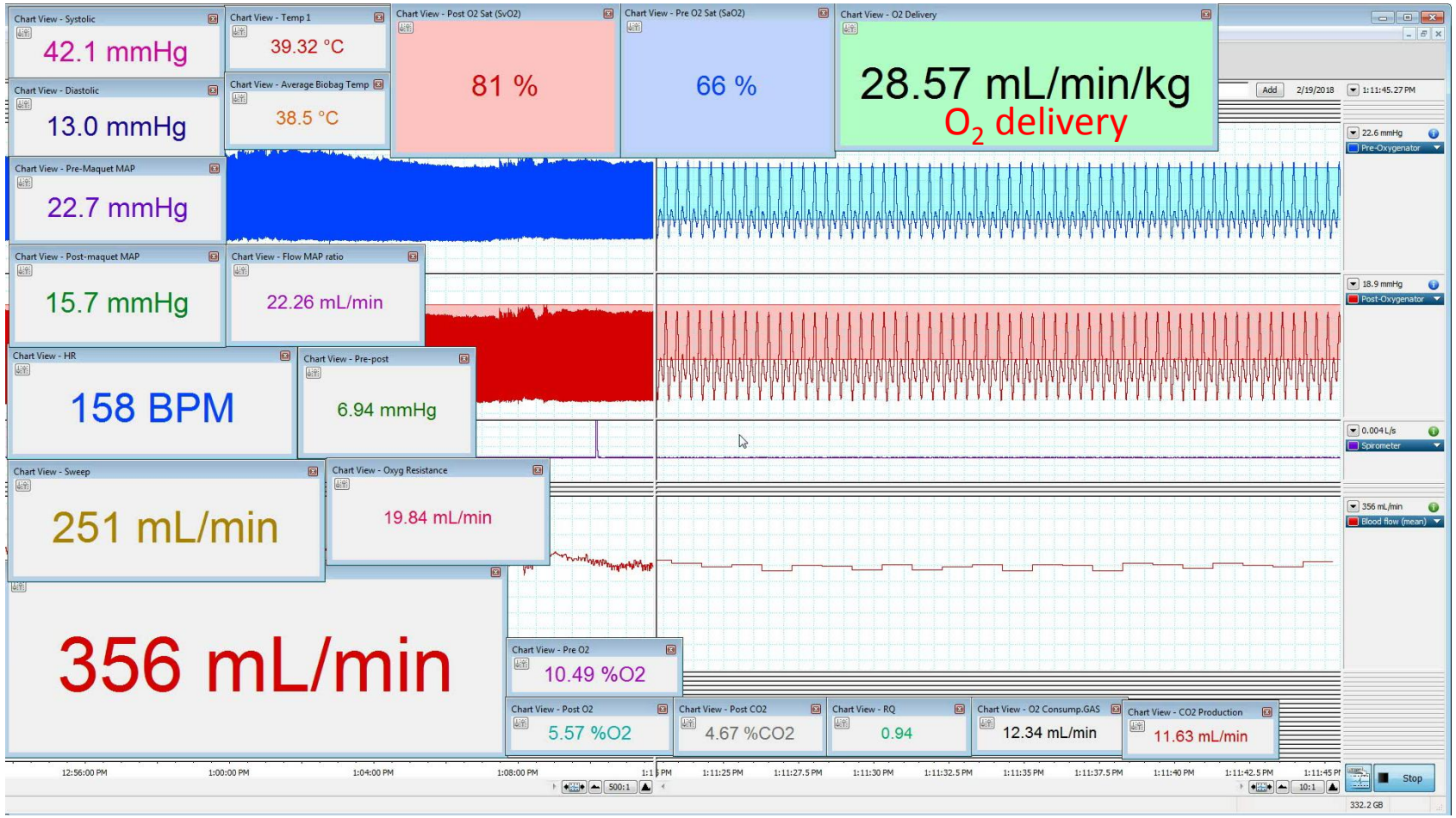
Somatic Growth and Maturation

Sheep
TPN
Lipids

107 Days of gestation

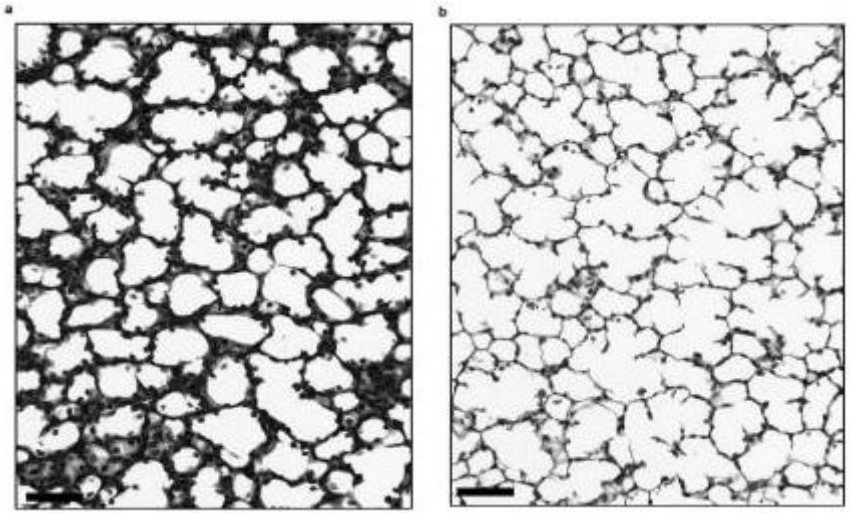
132 Days of gestation

Real-time patient monitoring

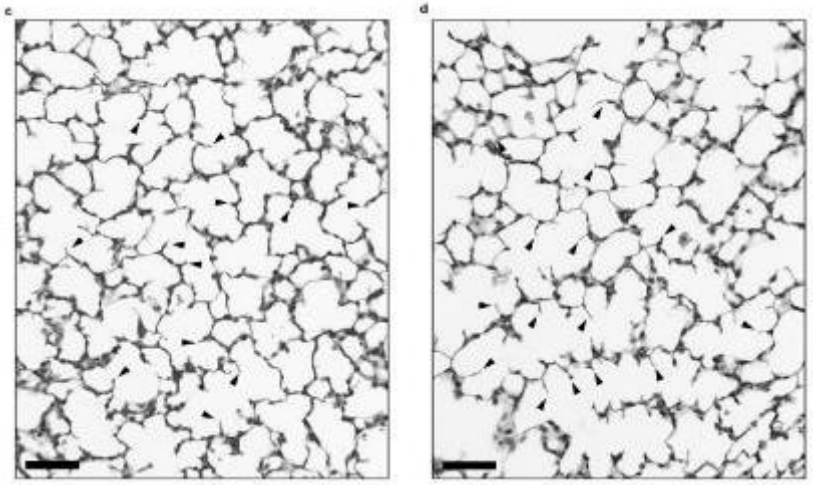


- Real-time O_2 delivery
- Oxygenator efficiency index

Lung development / respiratory function



113 D (preterm) 140 D (term)

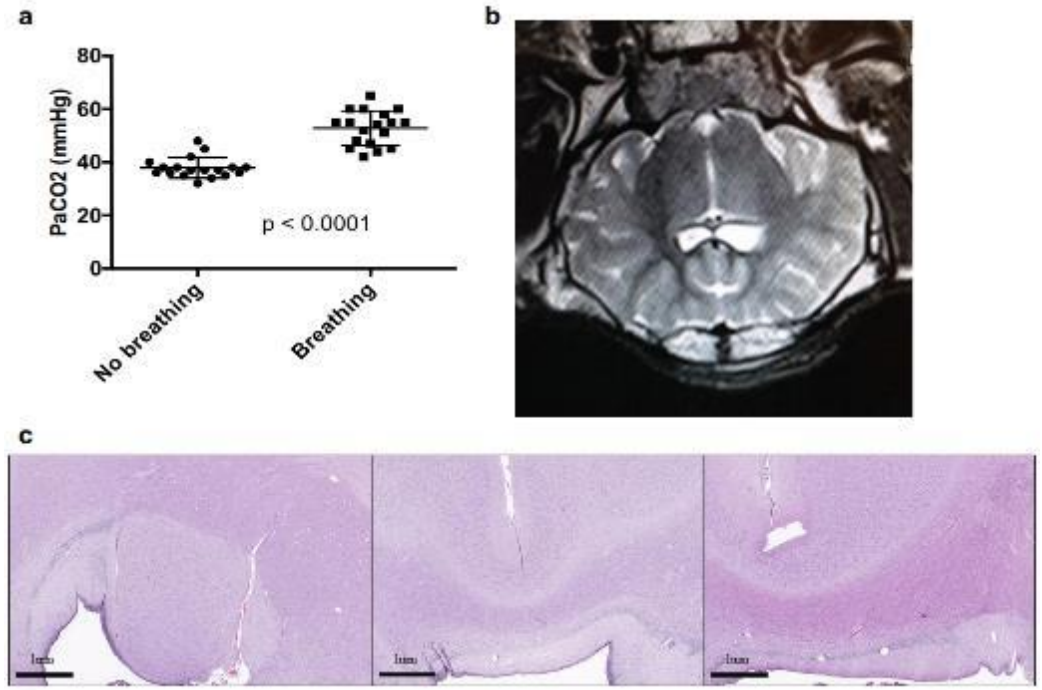


3-4 weeks of therapy

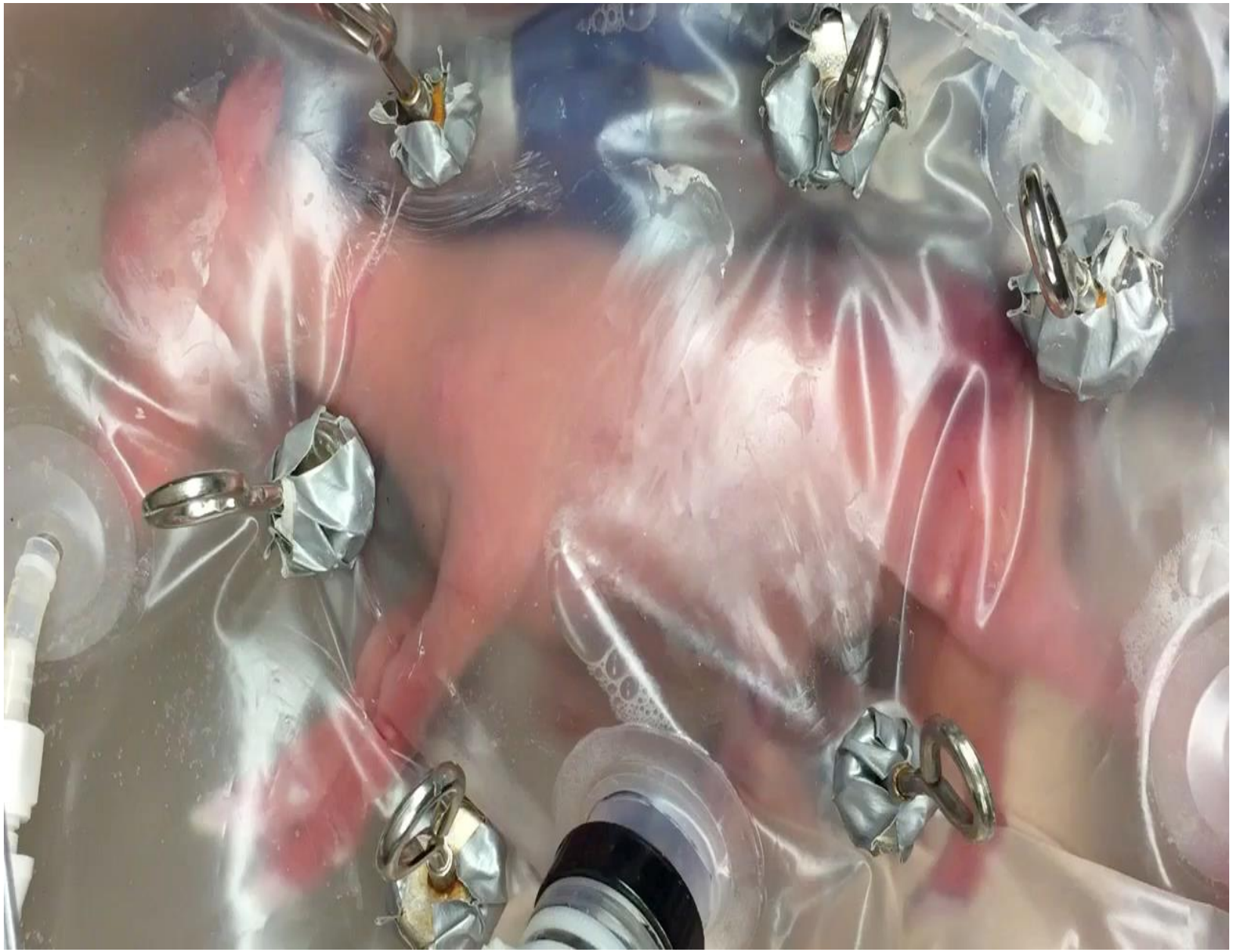
	Published Control (n=11)§	UA/UV (n=5)	Near-term Control‡ (n=3)
GA (days)	128	136±2	141±1
P_aCO_2 (mm Hg)	63±5	35±4	35±1
Resp Rate (bpm)	40	39±4	43±3
PIP (cm H_2O)	36±1	17±1	21±1
PEEP (cm H_2O)	3	5.5±0.2	5±0
pH	7.15±0.04	7.36±0.02	7.45±0.02
P_aO_2 (mm Hg)	197±29	128±12	143±24
f_iO_2 (%)	100	33±1	32±2
PIP (cm H_2O)	36±1	18±2	22±1
PEEP (cm H_2O)	3	5.7±0.2	5±0
A-a gr (mm Hg)	437	59±11	38±11

Life beyond EXTEND

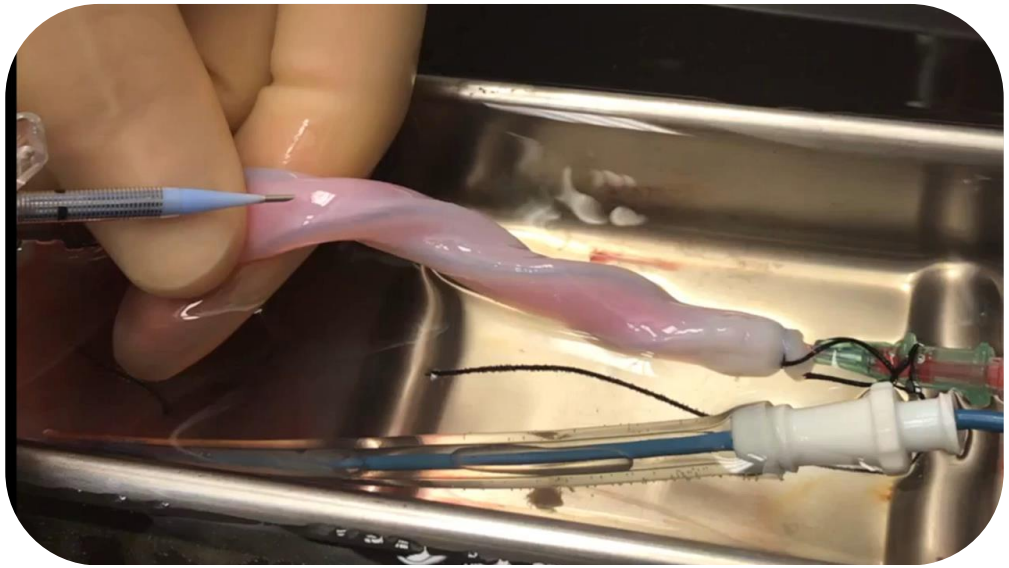
Normal neurological function & development



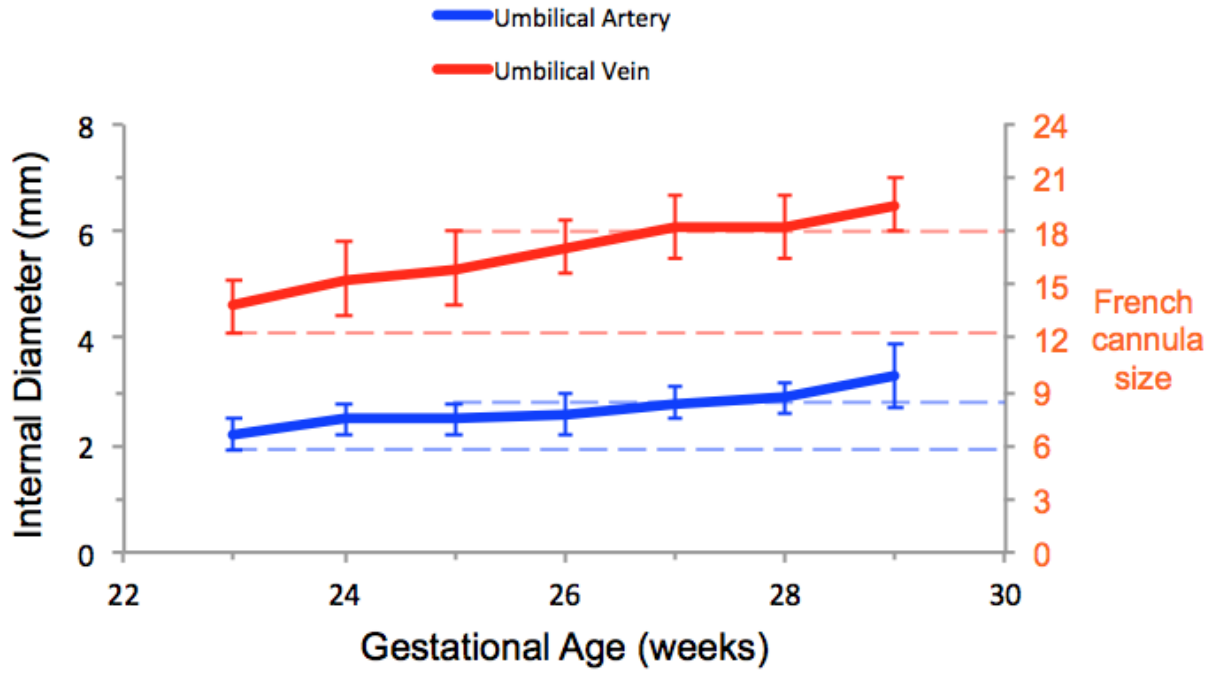
Size equivalence 24 wks (0.5 kg)



Screening clinical prototypes

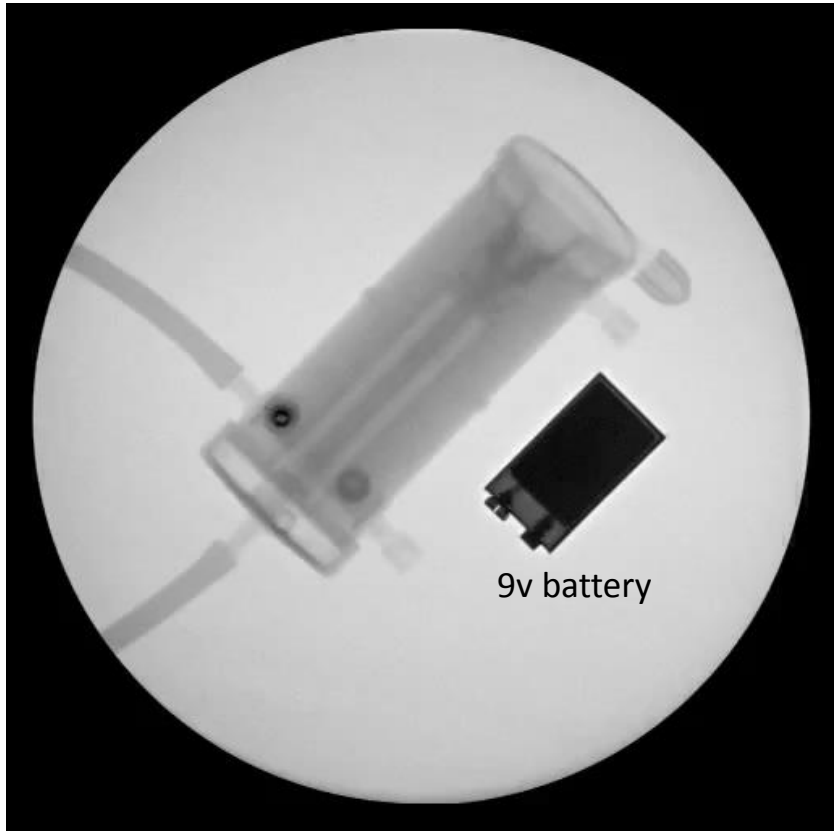


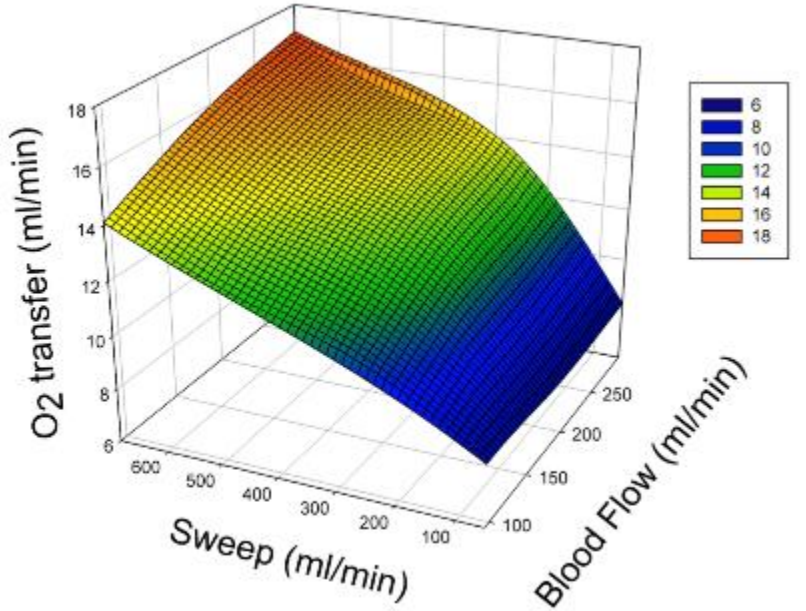
Human cord @ 22wks

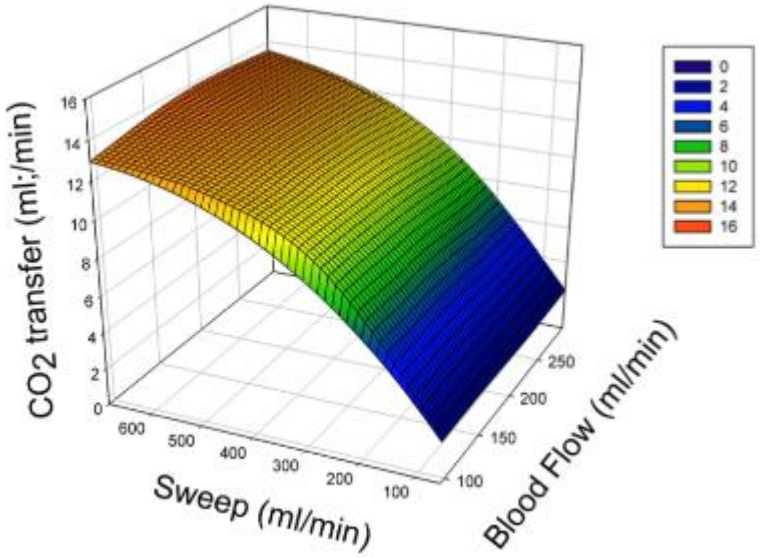


Prototyping membrane oxygenators

- blood transit times
- Priming volume
- gas exchange capacity







From Barn to Beside :

the path to clinical translation

Device design concept

Mobile

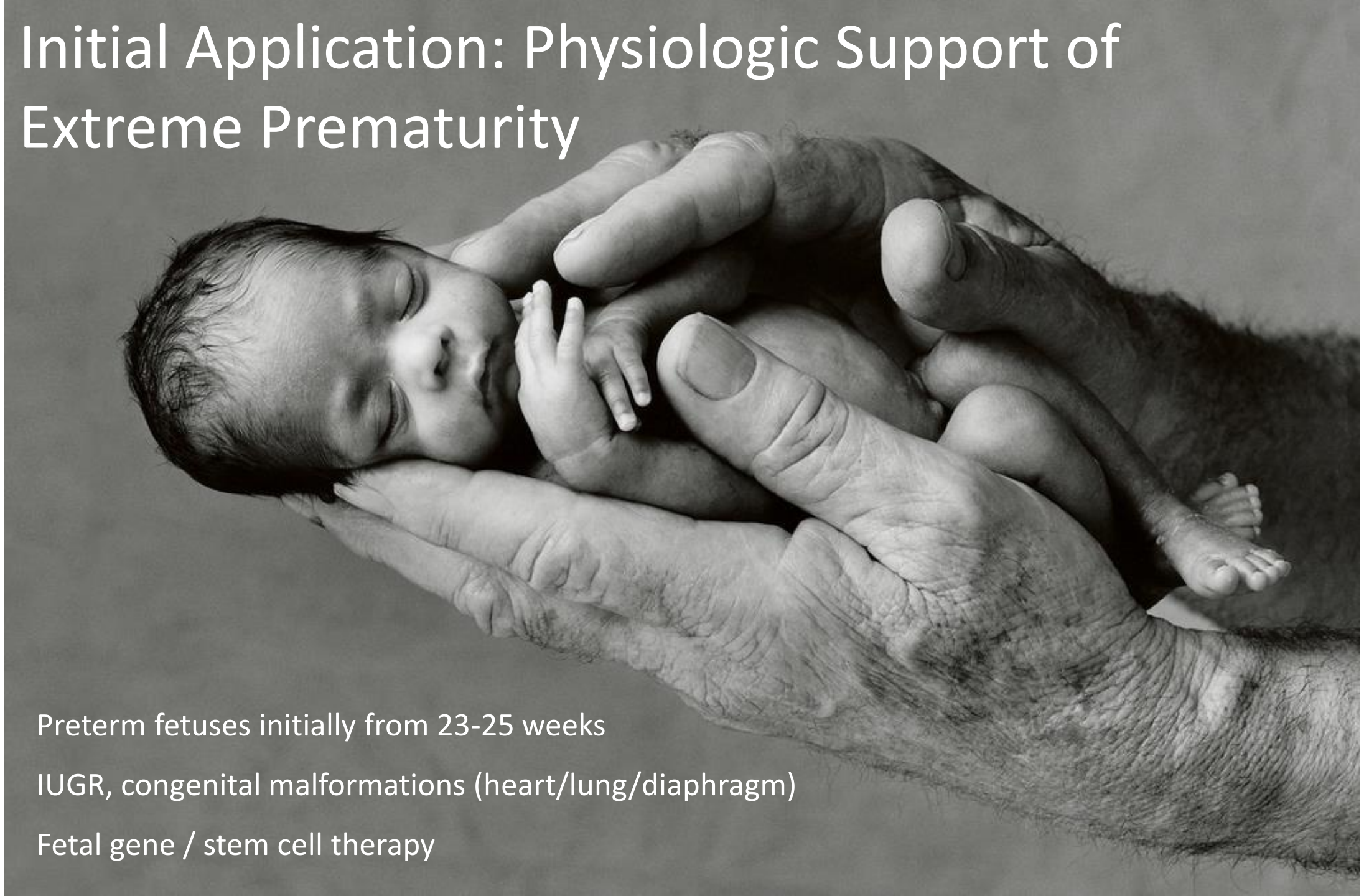
Sweep gases

Amniotic Fluid Bags

Ultrasound

Camera

Initial Application: Physiologic Support of Extreme Prematurity



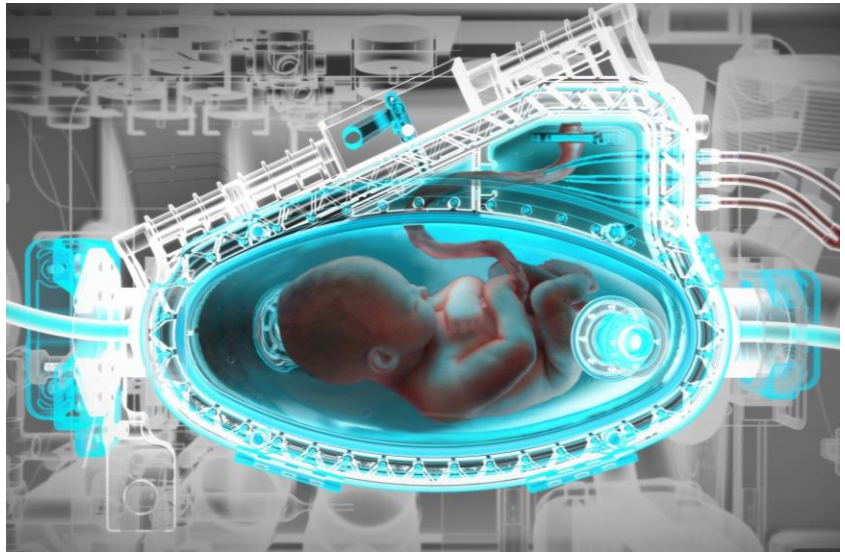
Preterm fetuses initially from 23-25 weeks

IUGR, congenital malformations (heart/lung/diaphragm)

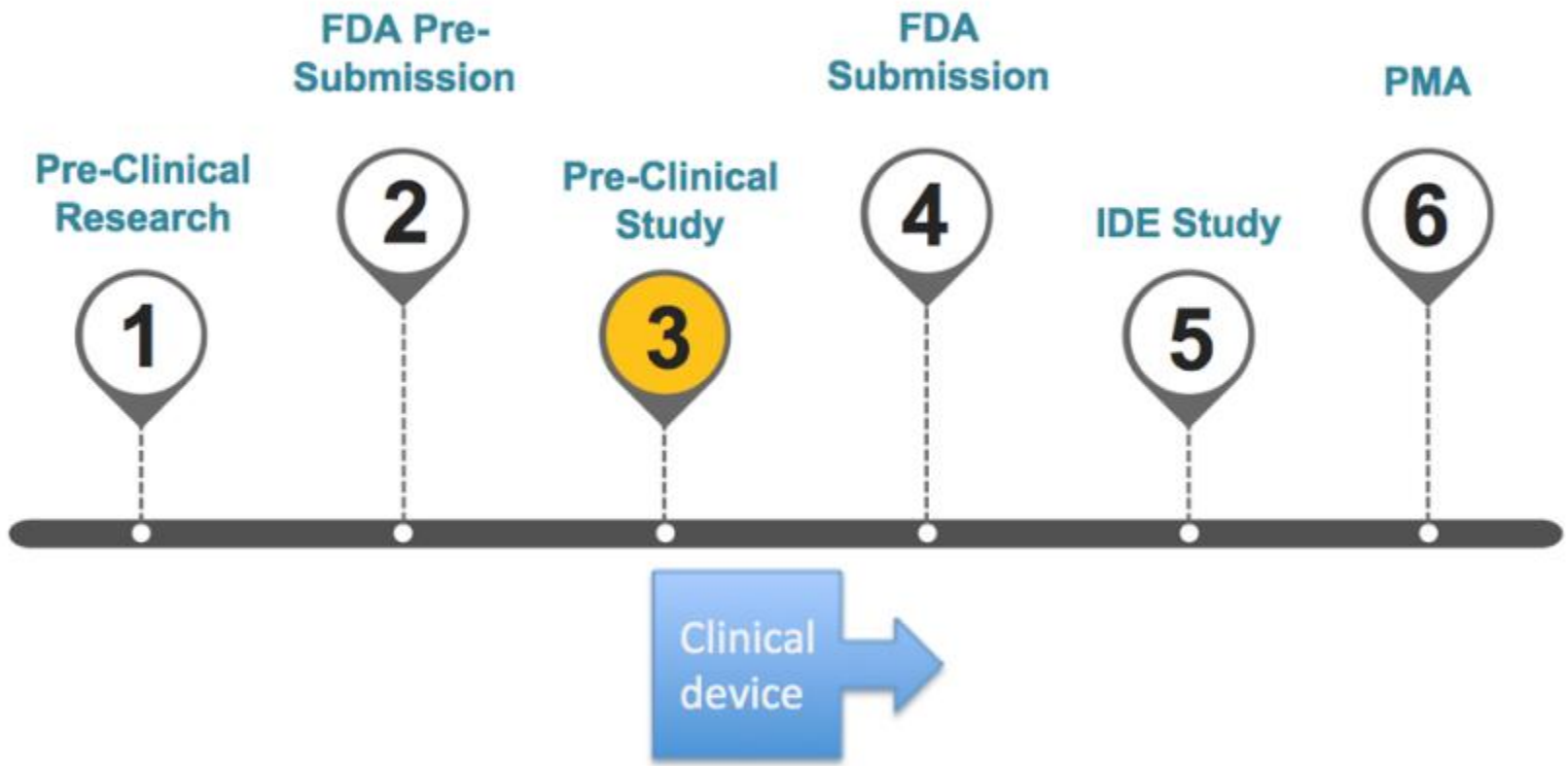
Fetal gene / stem cell therapy

A paradigm shift in neonatal care

Current NICU Care	EXTEND
Intubation / suctioning	n/a
mechanical ventilation with high FiO_2	n/a
repositioning ➔ head molding	n/a; biopod rotation Q12
skin assessment	n/a; BW ~10% submerged
diaper change, bathing, oral care	n/a
External noise / light	none to minimal
Oral care	n/a



Regulatory Roadmap



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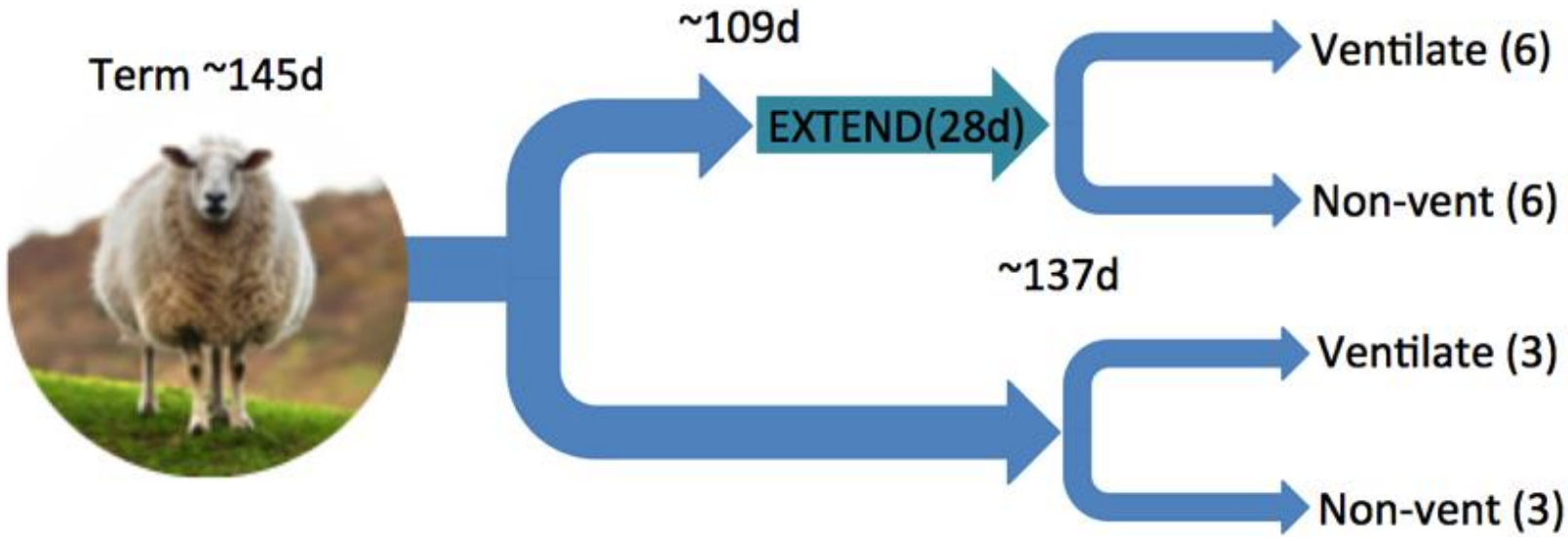
Regulatory / FDA Compliance / Animal Testing Partner

Preclinical animal study at CHOP



Initiated : Feb 2018 (18-24 months duration)

"Wins" with the FDA
GLP-like
No long-term neurological follow-up

The Key to success

The "LICU"

Children's Hospital of Philadelphia℠

BREAKTHROUGHS. EVERY DAY.