

# Lung Maturation and RDS – 2018

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# Conflicts of Interest Declaration

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**Source:**

**Purpose:**

Grants

B&M Gates Foundation

Antenatal steroid studies

GSK (Matt Kemp)

Steroid Pharmacokinetics

Gifts for Research

Chiesi

Surfactant

Merck

Betamethasone

Fisher & Paykel

Respiratory Supplies

Consulting

B&M Gates Foundation

Infant mortality in low resource environments

Chiesi

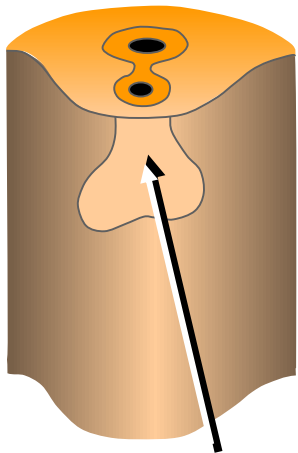
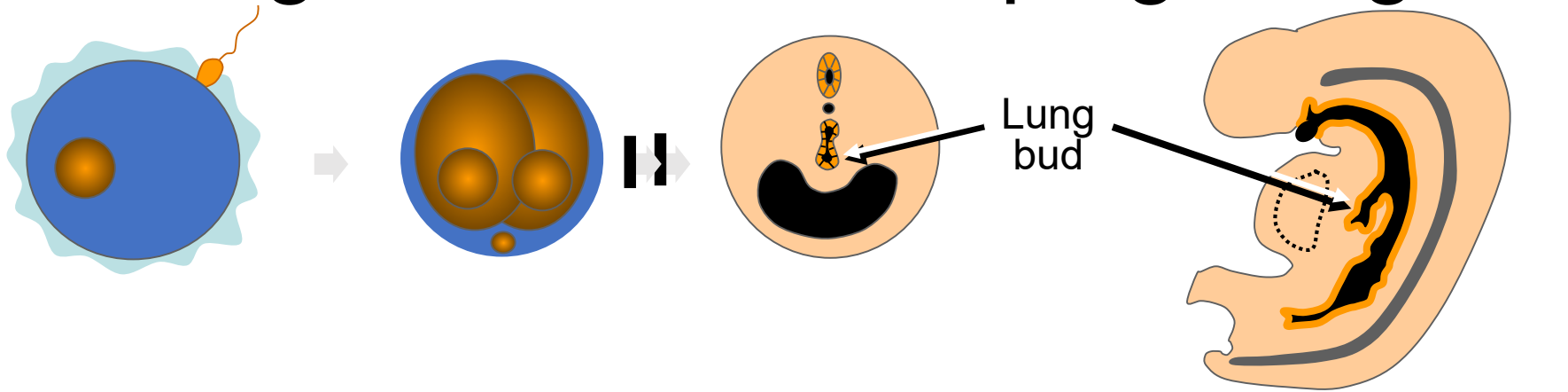
New treatments for BPD

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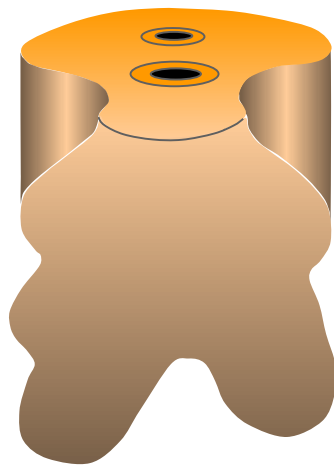
# Goals for Presentation

- A 2018 view of lung development / maturation
- RDS – a normal result of prematurity
- Induced lung maturation: inflammation and Antenatal Steroids
- What is RDS in 2018?

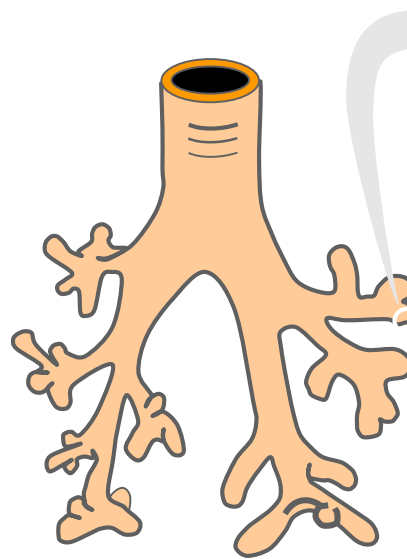
# Stages of the Developing Lung



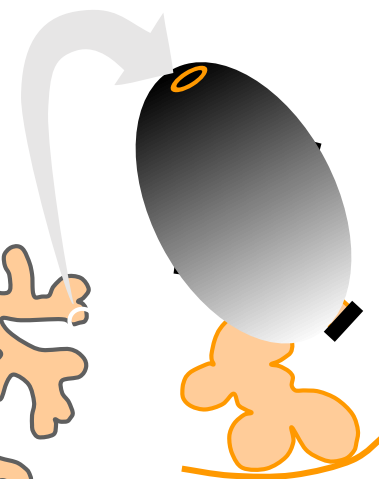
I. Embryonic



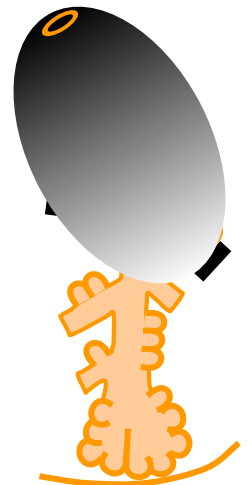
II. Pseudoglandular



III. Canalicular

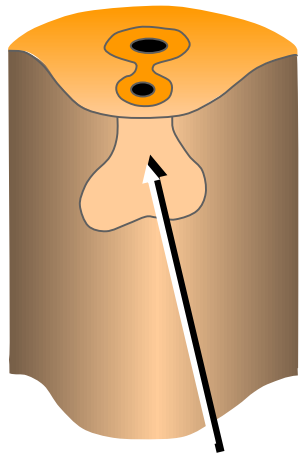
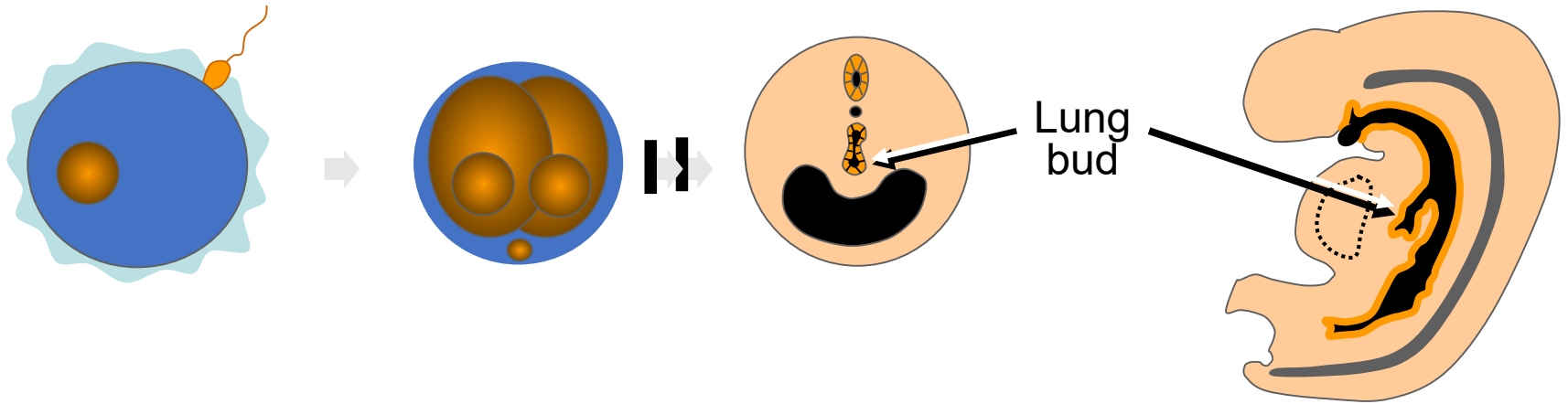


IV. Saccular

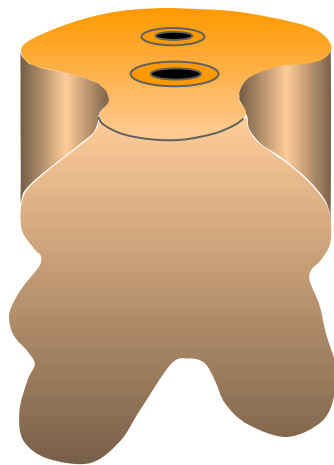


V. Alveolar

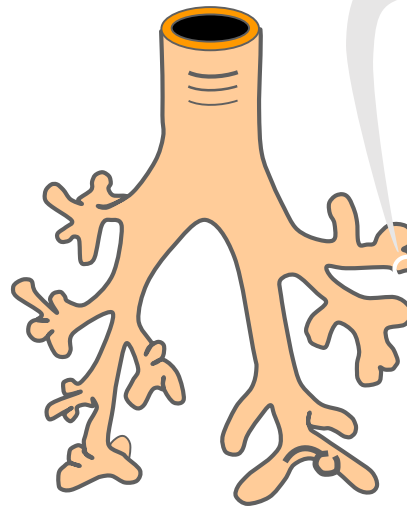
# Canalicular, Saccular, Alveolar



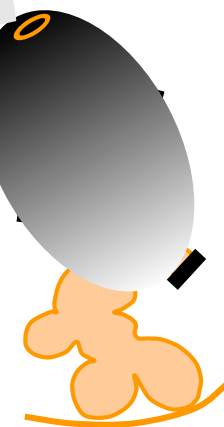
I. Embryonic



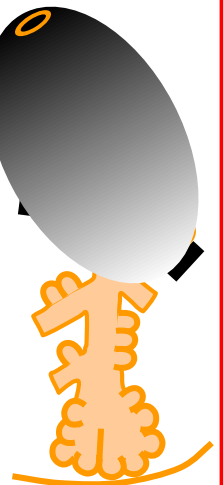
II. Pseudoglandular



III. Canalicular



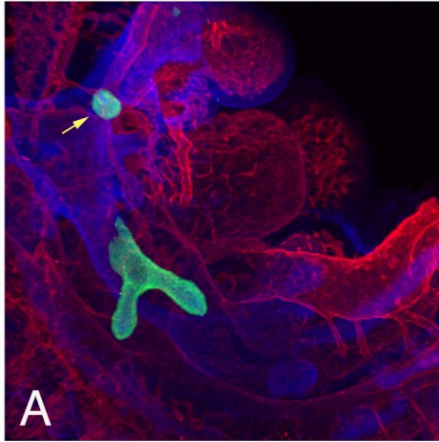
IV. Saccular



V. Alveolar

# Lung Morphogenesis: Mice and Humans

John Shannon  
CCHMC



## Lung Bud Initiation

Human 21-28 days

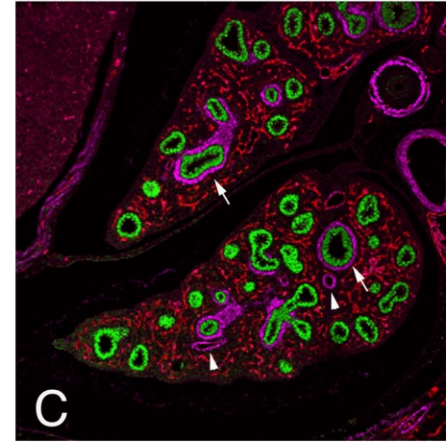
Mouse 9 days



## Embryonic

Human 3-7 wks

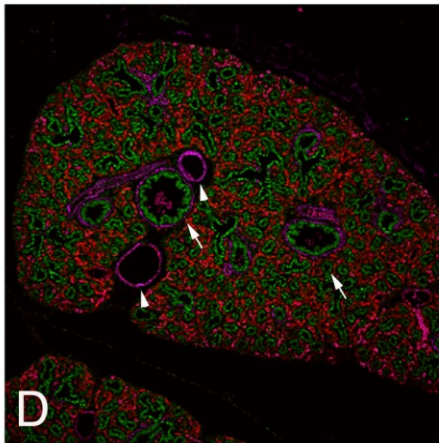
Mouse 9-12 days



## Pseudoglandular

Human 5-17 wks

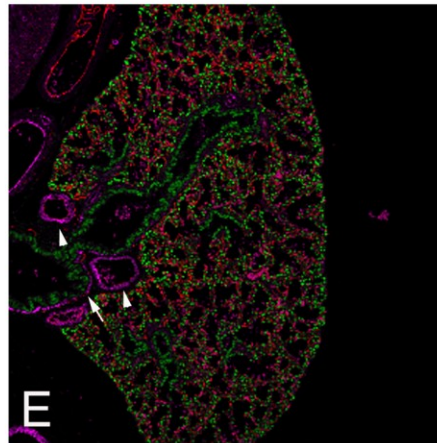
Mouse 12-16 days



## Canalicular

Human 16-26 wks

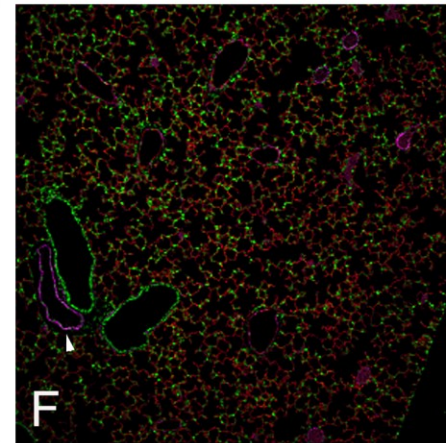
Mouse 16-17 days



## Saccular

Human 24-38 wks

Mouse 17 days to 5 days postnatal



## Alveolar

Human 36 wks to 18 months postnatal

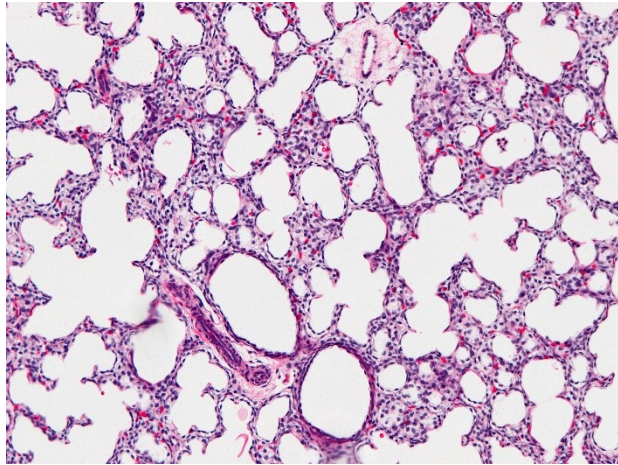
Mouse 5-14 days postnatal

# Normal Lung Development in Rhesus at Gestations Relevant to RDS

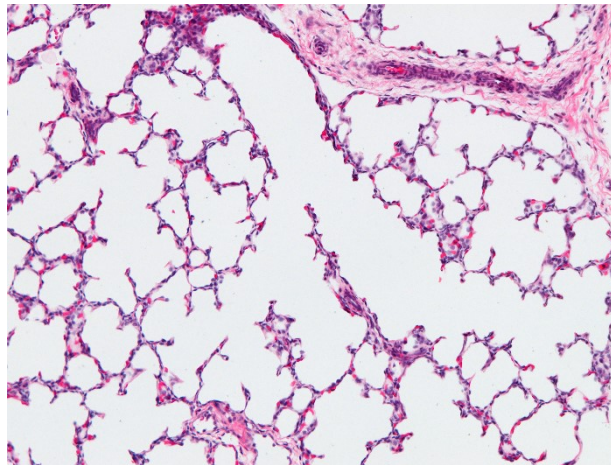
65% Gestation

79% Gestation

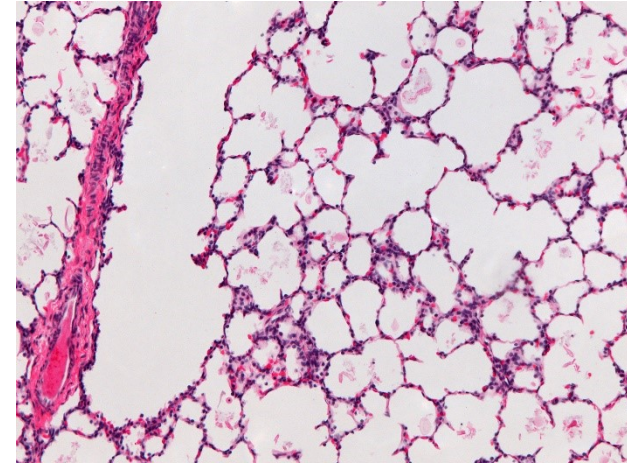
94% Gestation



GA105



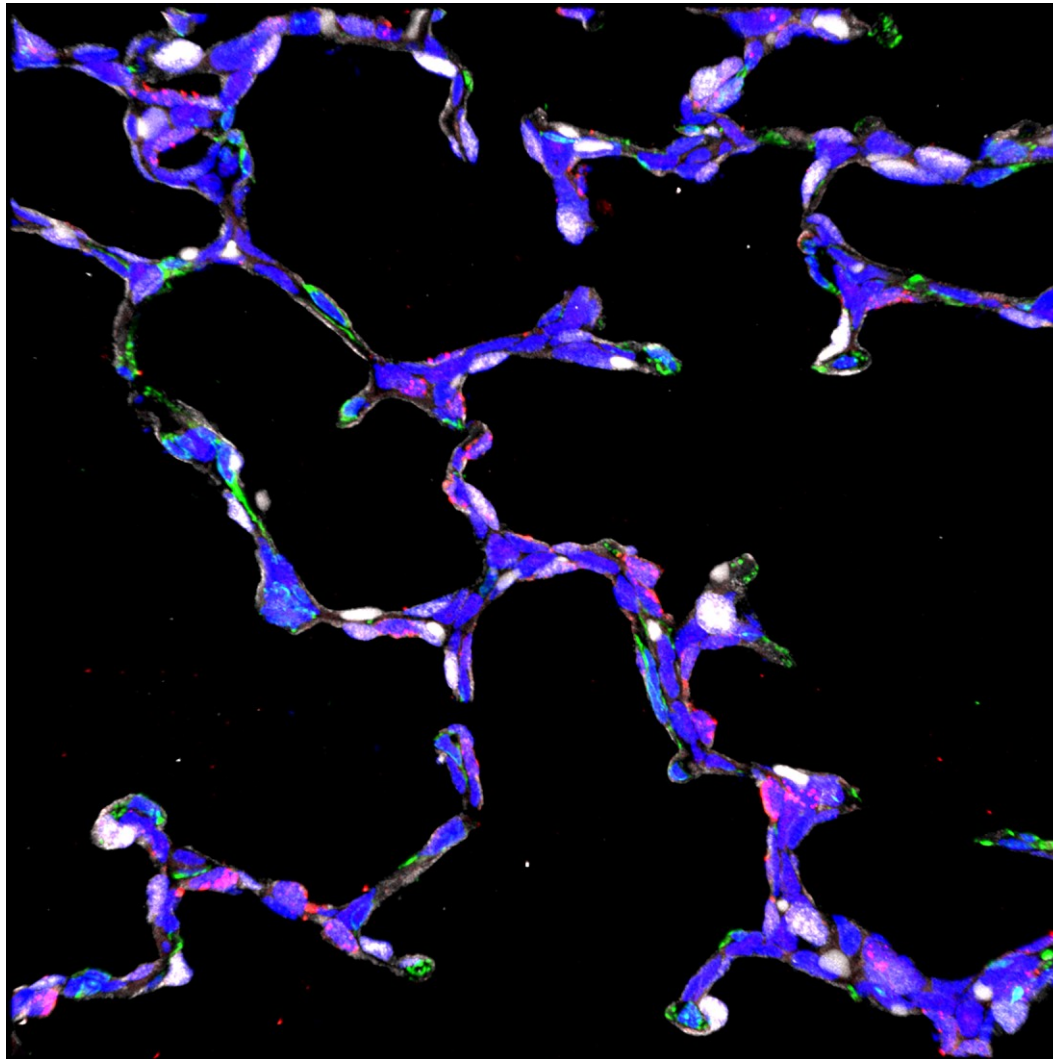
GA130



GA150

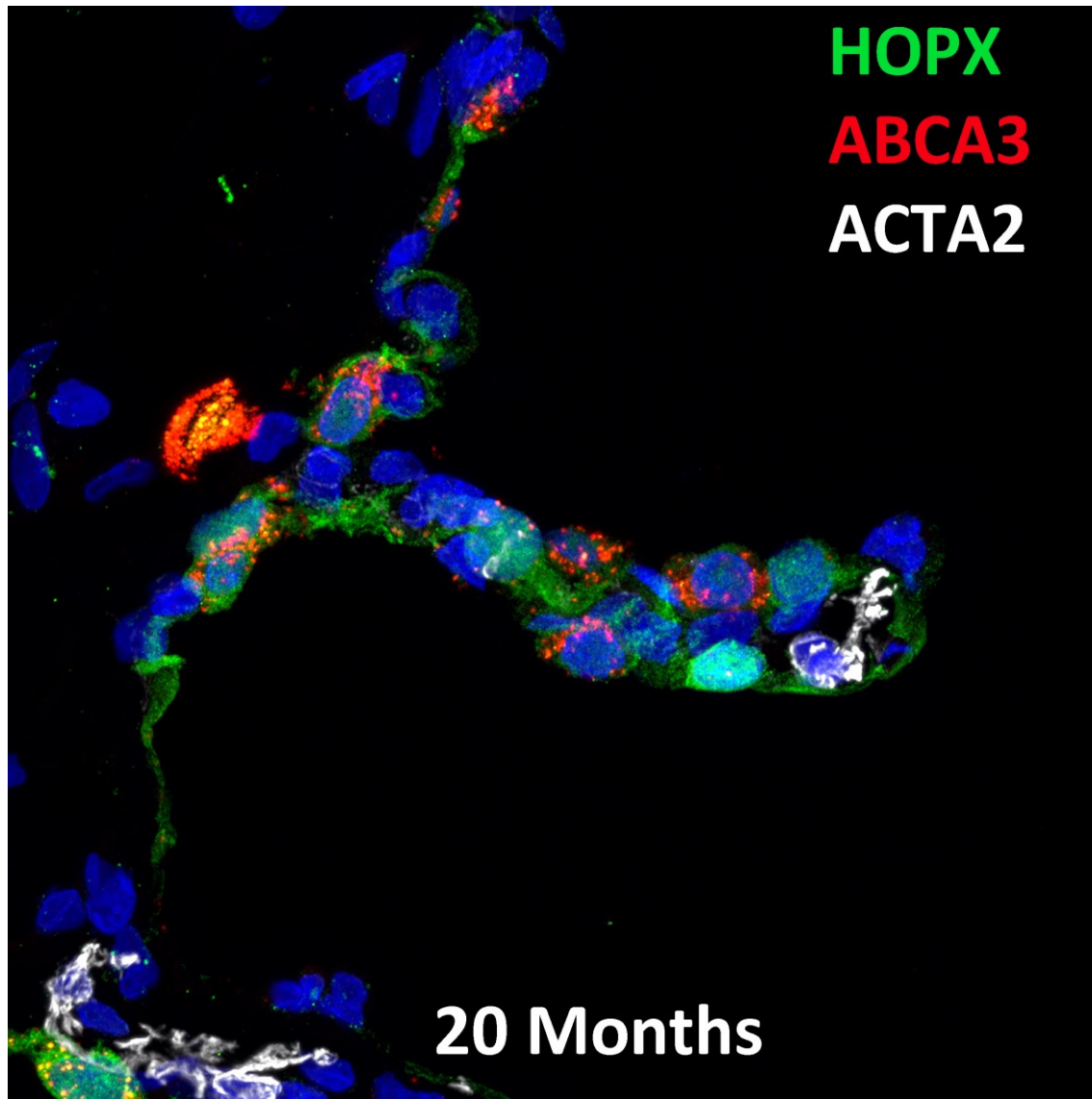
LungMAP

# Alveolar Septa: 130d GA (79% Term) Preterm Rhesus



LungMAP

# Alveolar Septa: Human



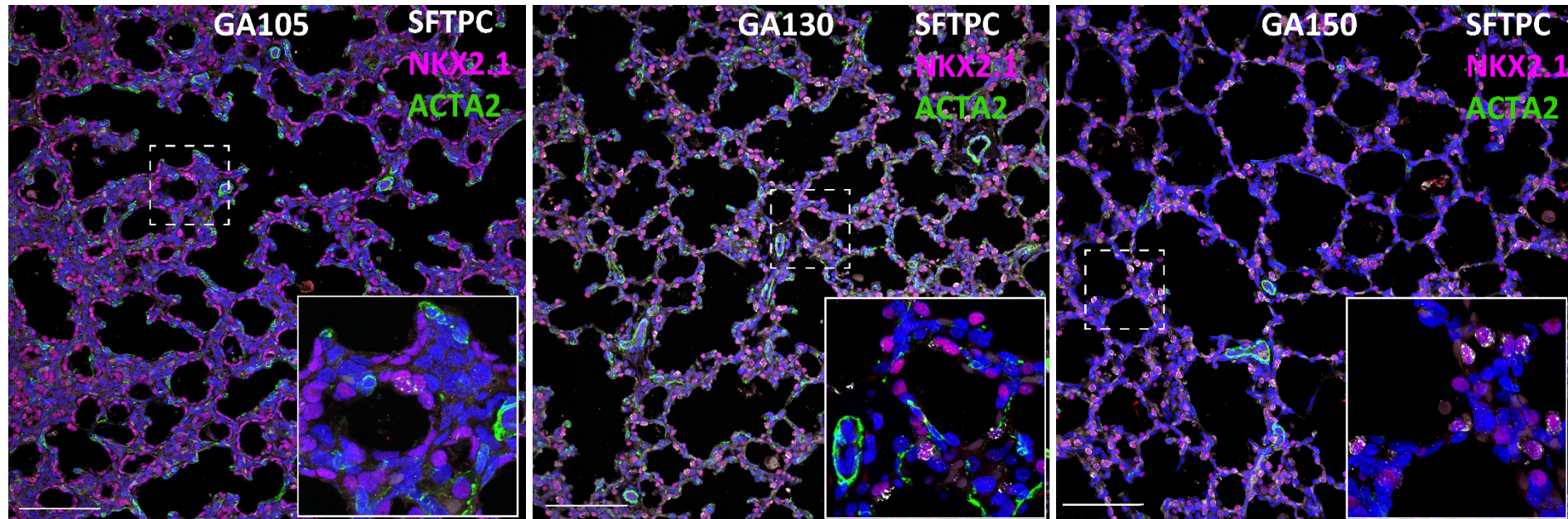
- Type 1 cells
- Type 2 cells
- Actin smooth muscle

# Fetal Rhesus macaque – immunolabeling for SP-C, Epithelial Cells, and Smooth Muscle Actin

65% Gestation

79% Gestation

94% Gestation

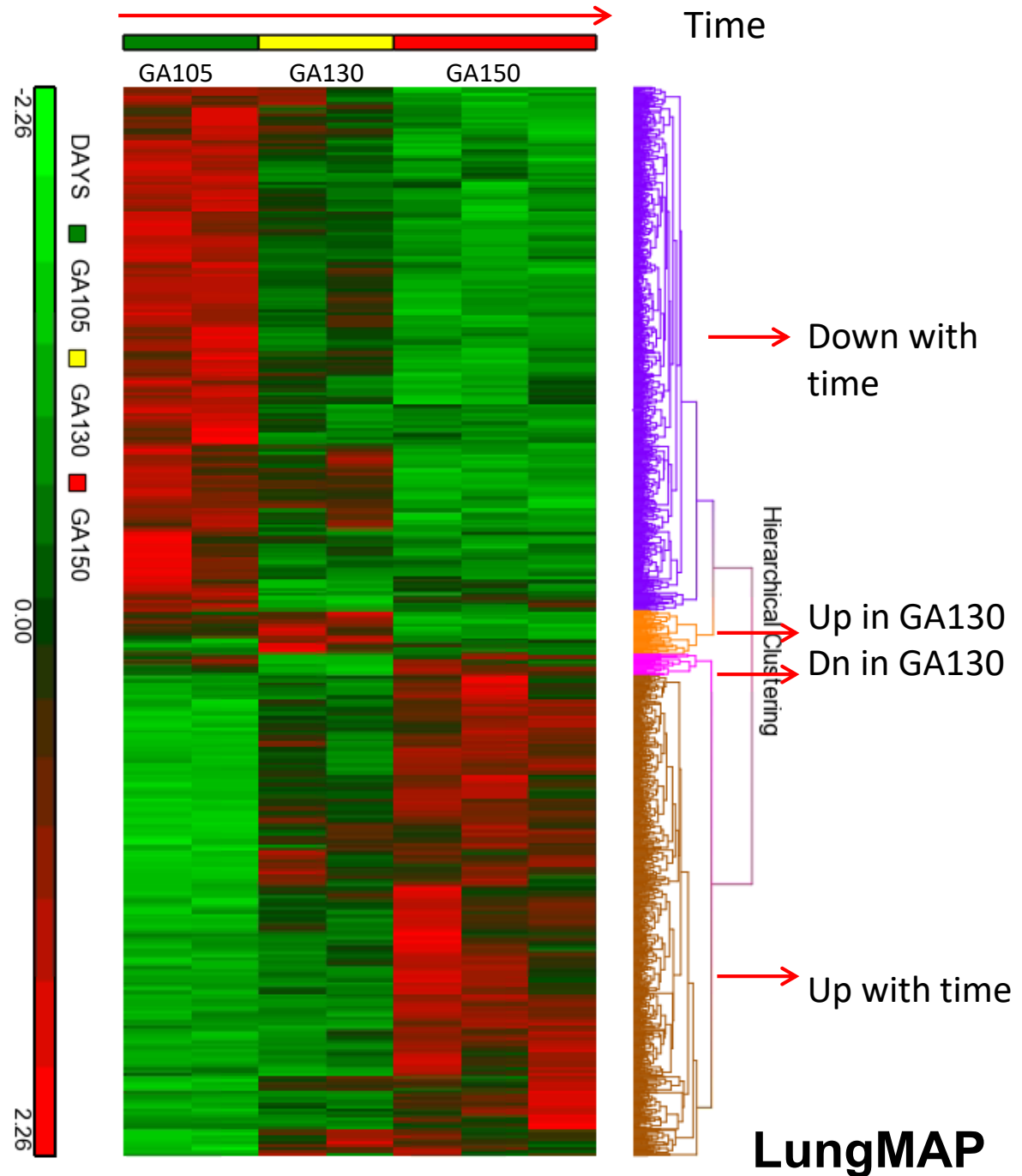


**SFTPC – Surf. Protein C**  
**NKX2.1 – TTF-1 – Type 2 cells**  
**ACTA2 – Smooth muscle actin**

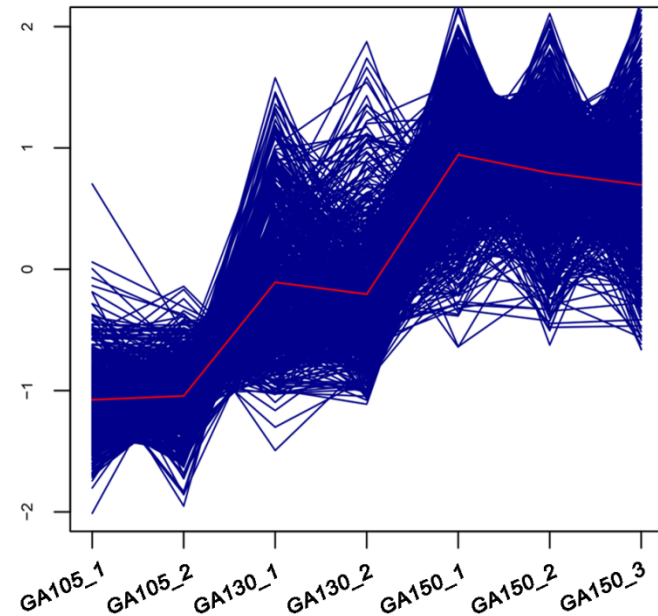
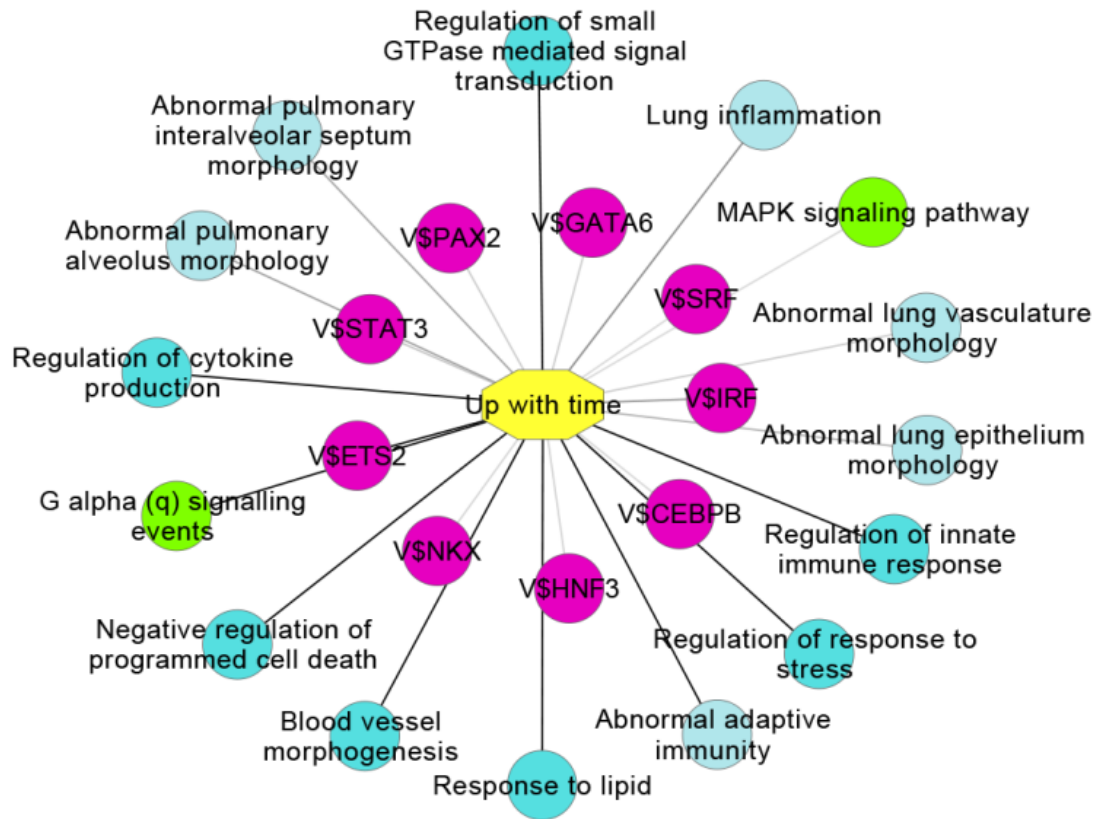
**LungMAP**

# RNA Seq- Rhesus Lung at 105/130/150d gestation

## Hierarchical clustering



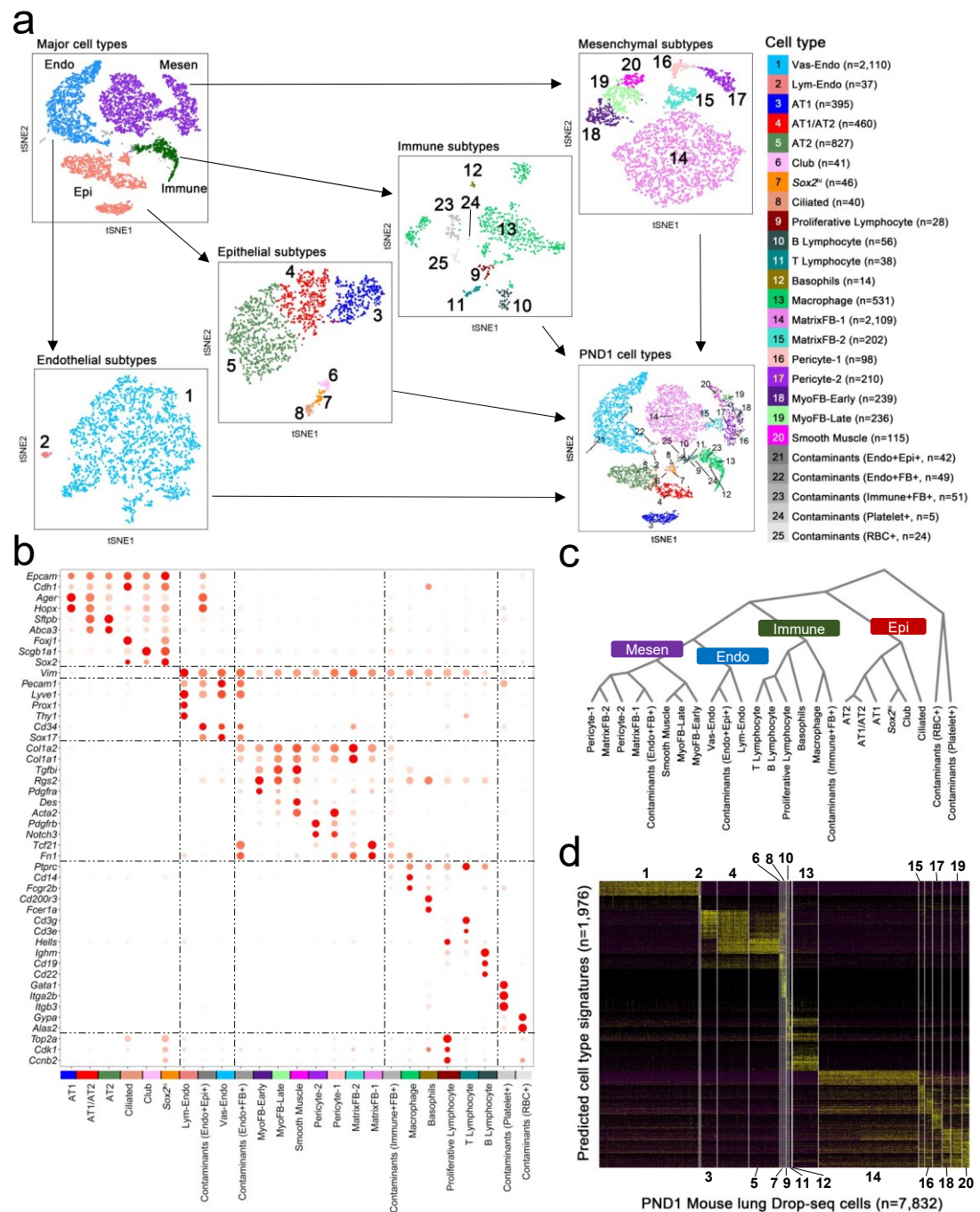
# Up with Time: Gene expression increasing with gestational age



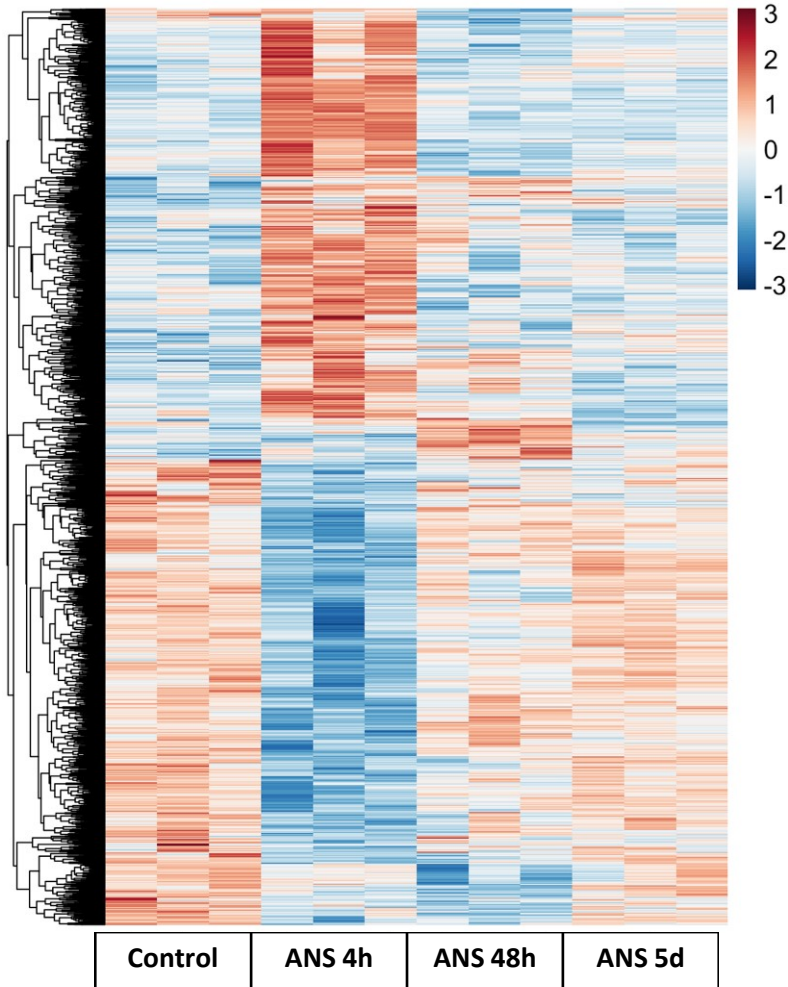
Immunity/Surfactant/Alveolar Development

# Single cell Drop Seq of 1 day mouse lung

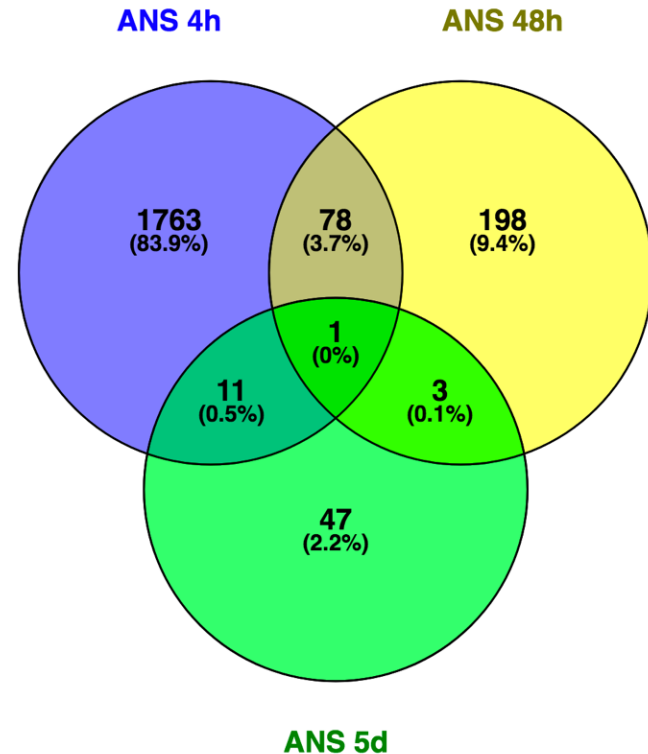
Whitsett - Unpublished



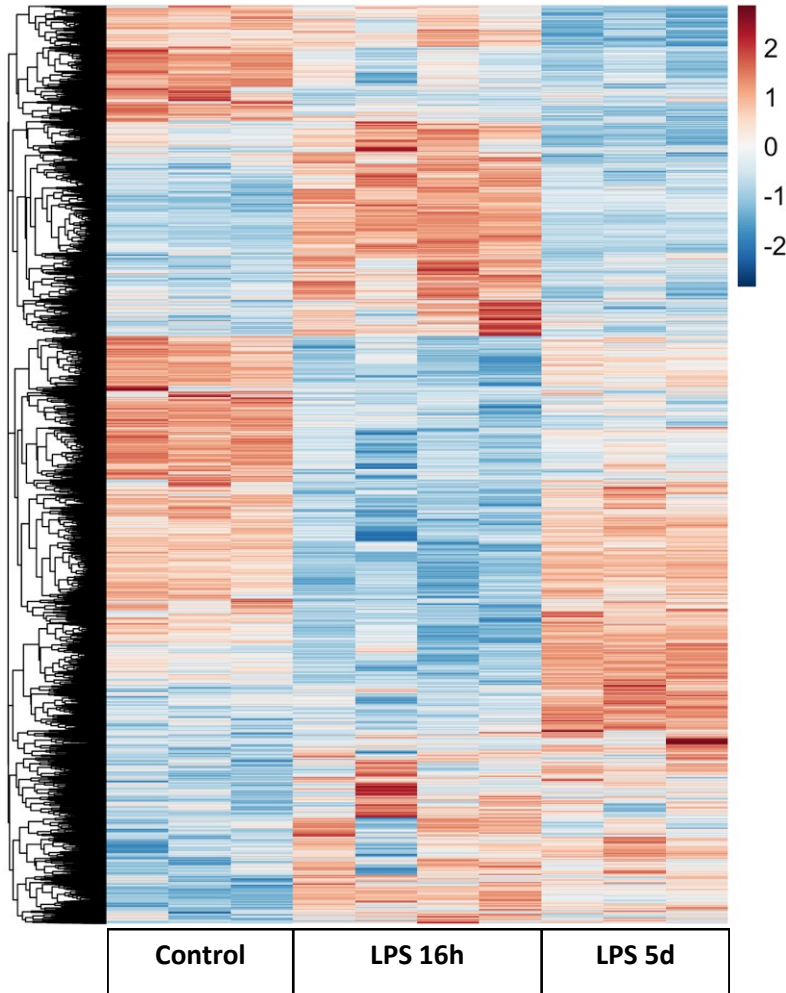
# mRNA Seq. of Lung



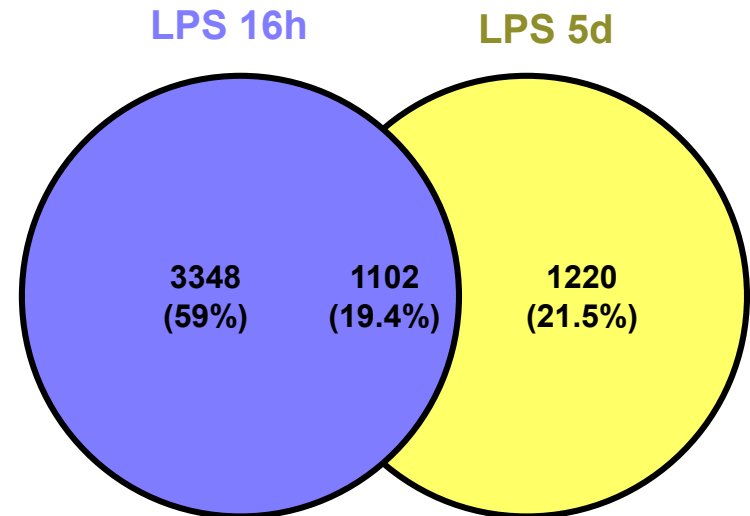
Rhesus treated with antenatal steroids (Celestone - 0.25 mg/kg)



# mRNA Seq. of Lung

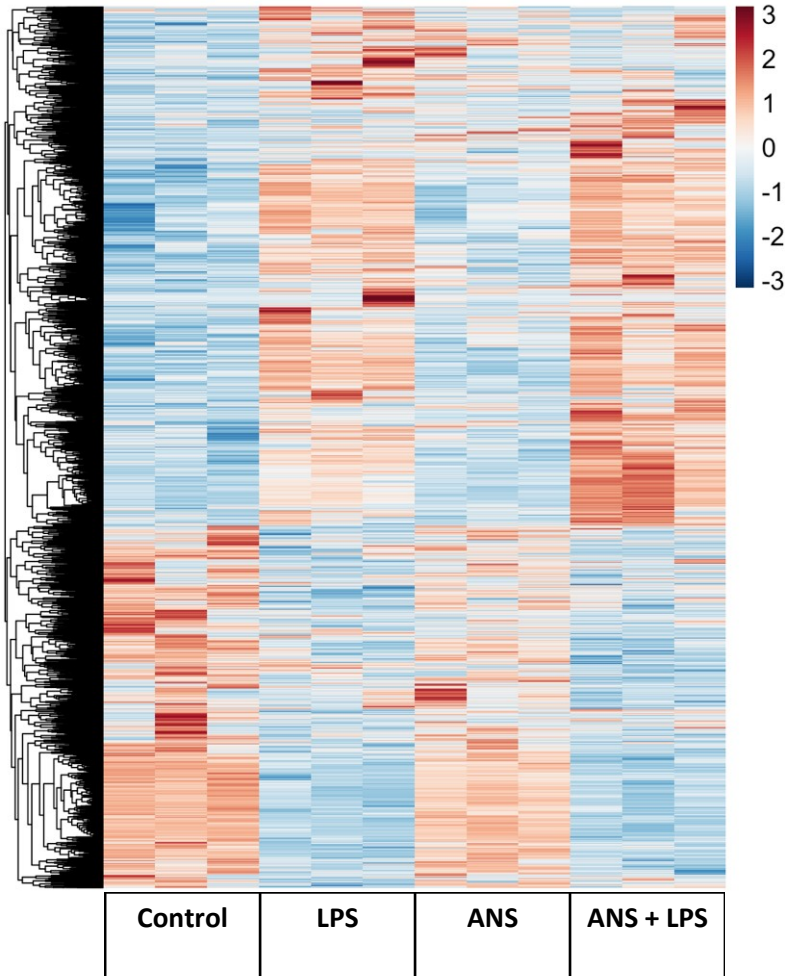


Rhesus treated with  
intraamniotic LPS

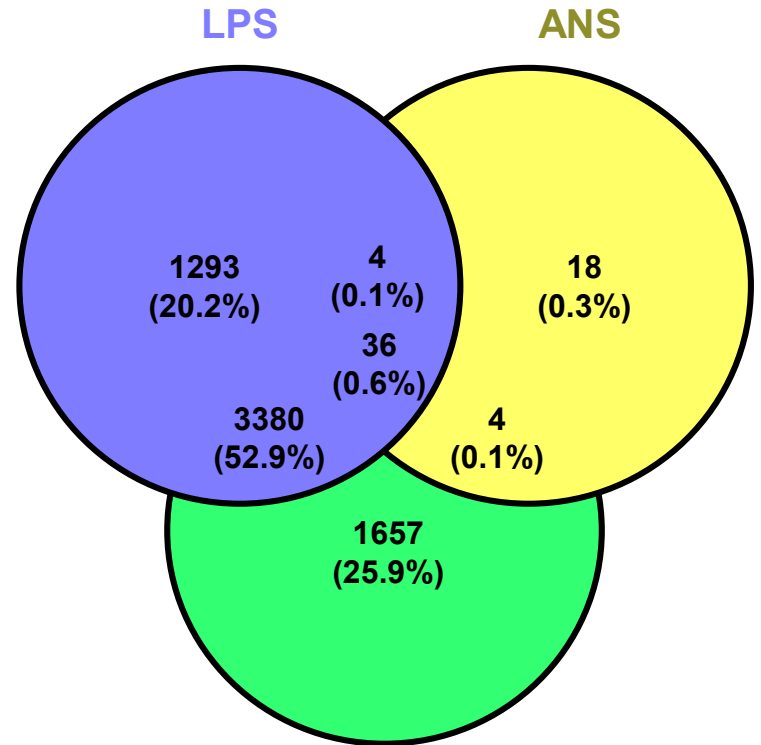


# mRNA Seq. of Lung

Rhesus treated with  
intraamniotic LPS, antenatal  
steroids or both



5 day exposures



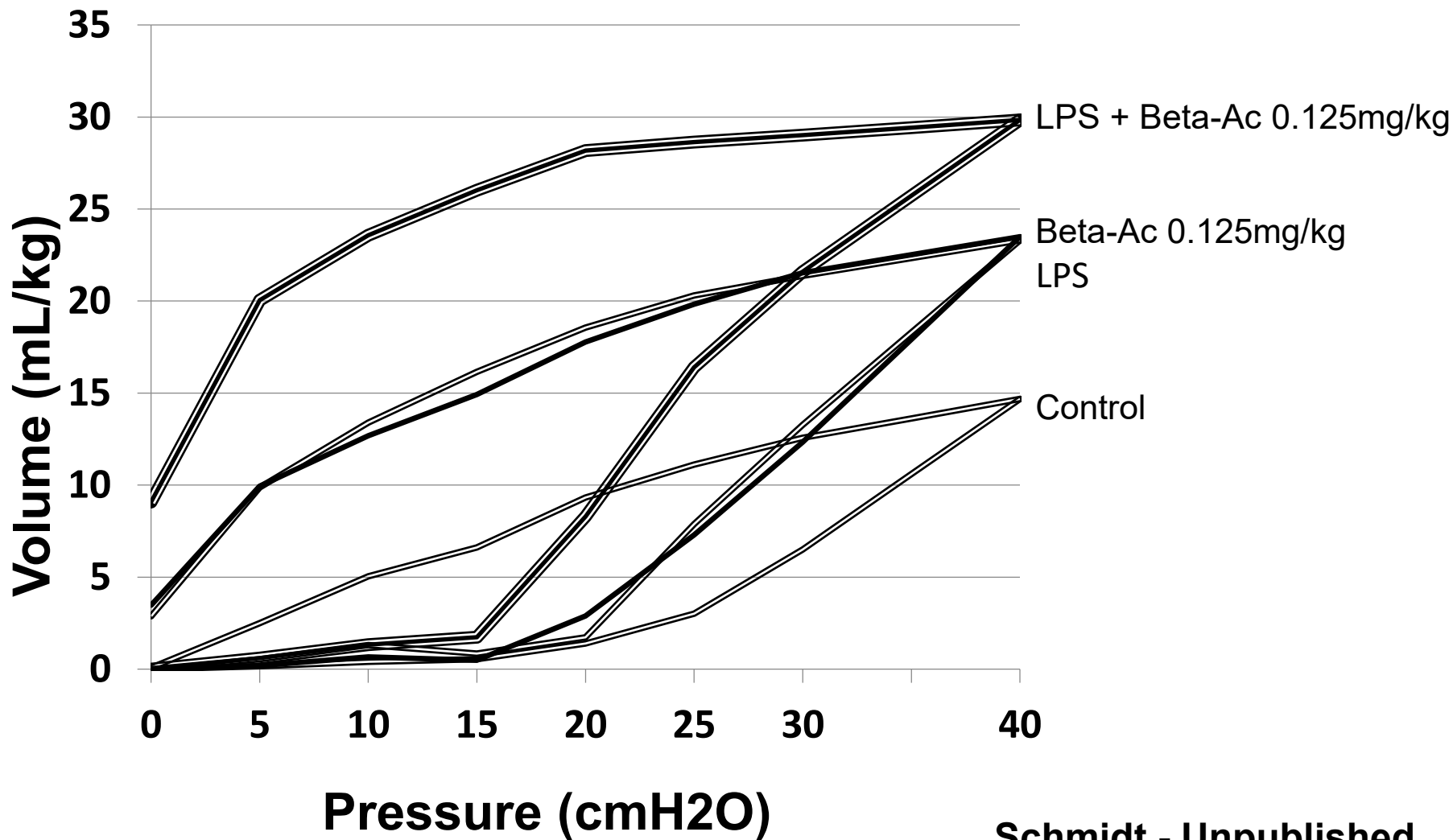
ANS+LPS

Schmidt - Unpublished

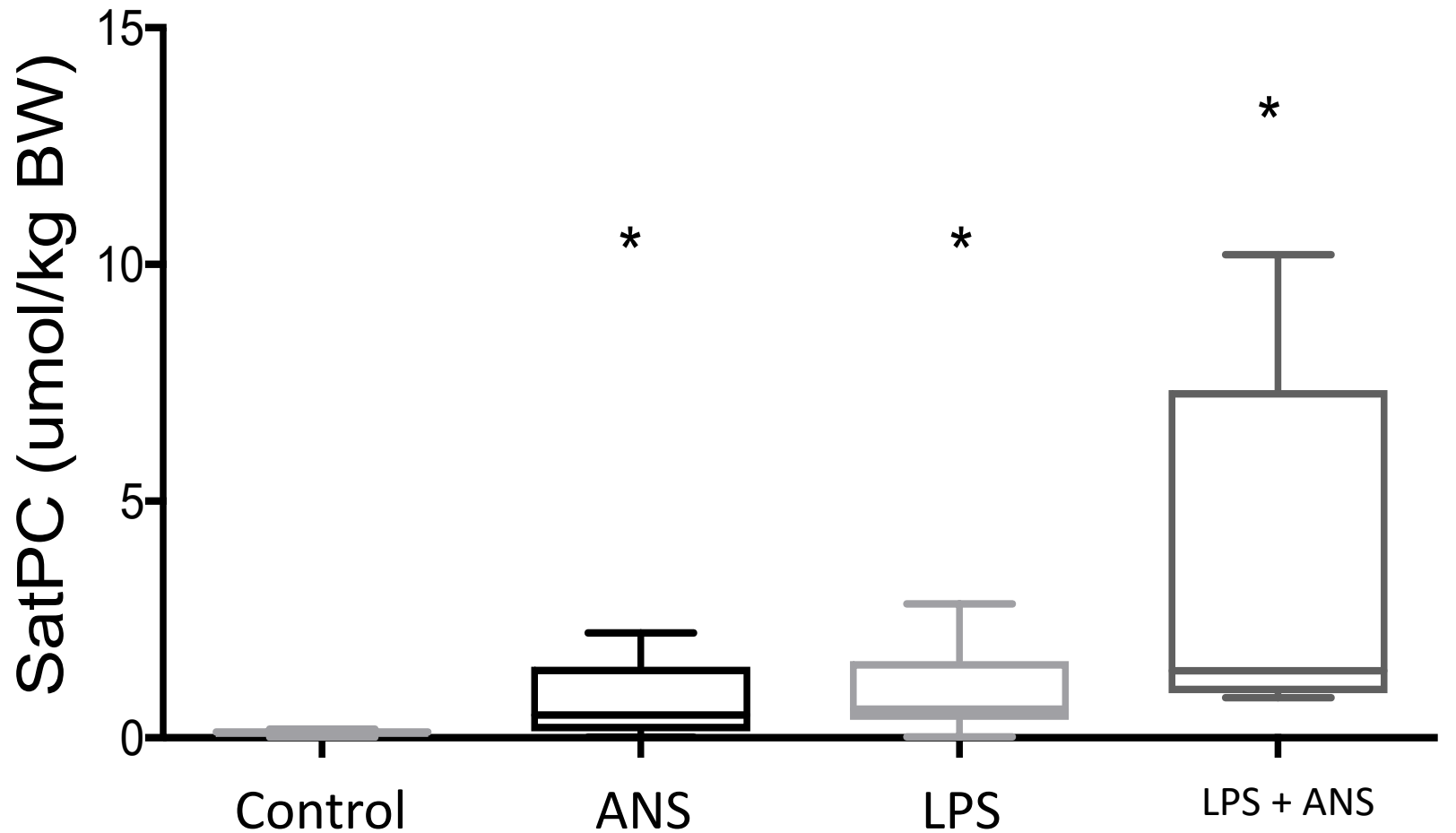
# Concepts from molecular lung maturation

- Arrays of genes and pathways participate in lung maturation.
- Complex distal lung structures contain multiple cell types, each with unique expression patterns.
- Cells are anatomically organized to cooperate in development.
- Each cell has a unique expression pattern.
- Antenatal steroids and inflammation are potent modulators of gene expression.

# Preterm Rhesus macaques exposed to IM Beta-Ac 0.125mg/kg vs IA LPS or IM Beta-Ac 0.125mg/kg + LPS



# Saturated PC in alveolar wash of fetal lungs - Rhesus



**The route problem: RDS is caused primarily by surfactant deficiency – and lung structural immaturity**

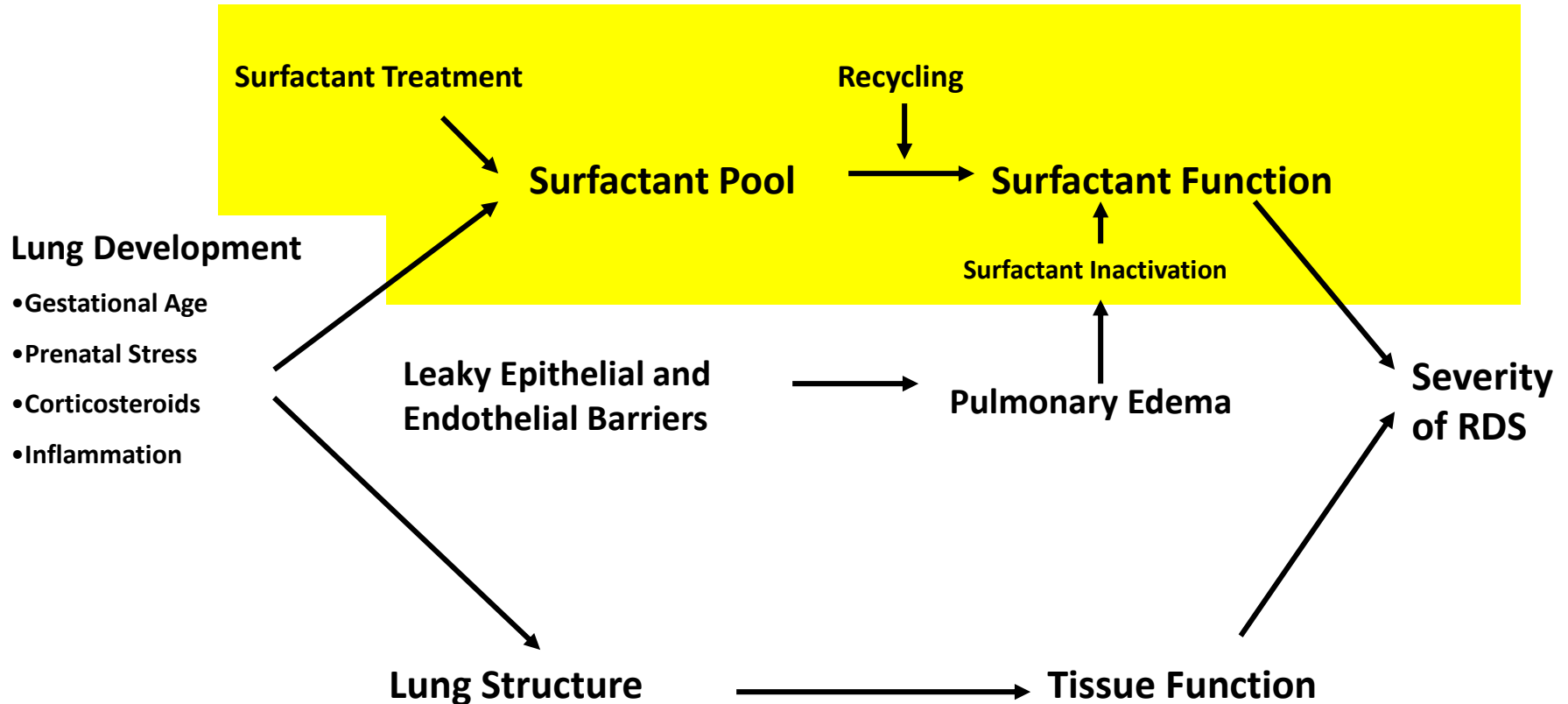
But we:

- Do not measure surfactant.
- Do not evaluate lung structure.

# What is RDS in 2018?

- Which infants are at risk of RDS?
- How do we diagnose RDS?
- Does treatment influence diagnosis?
- Should any babies die of RDS?

# Pathophysiology of RDS – 1990s



**No changes in this diagram in 30 years**

# Problems with the diagnosis of RDS in VLBW infants

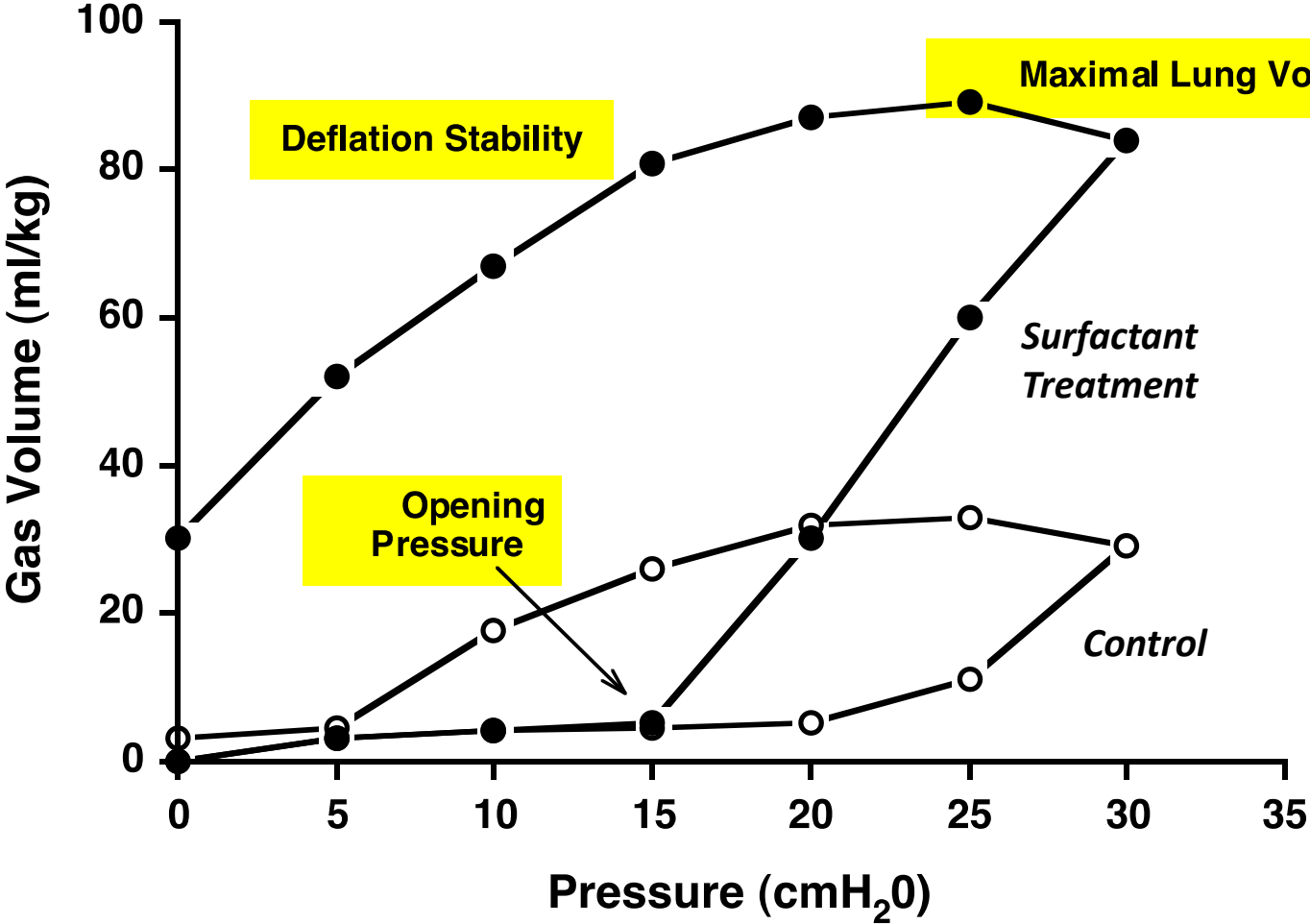
- Symptoms – tachypnea, retractions, flaring, grunting.
- Oxygen need – amount and time needed.
- Chest x-ray – uniform and granular, lung volume.

**A diagnosis of exclusion - RDS if the infant does not have infection, pulmonary hypoplasia, TTN.**

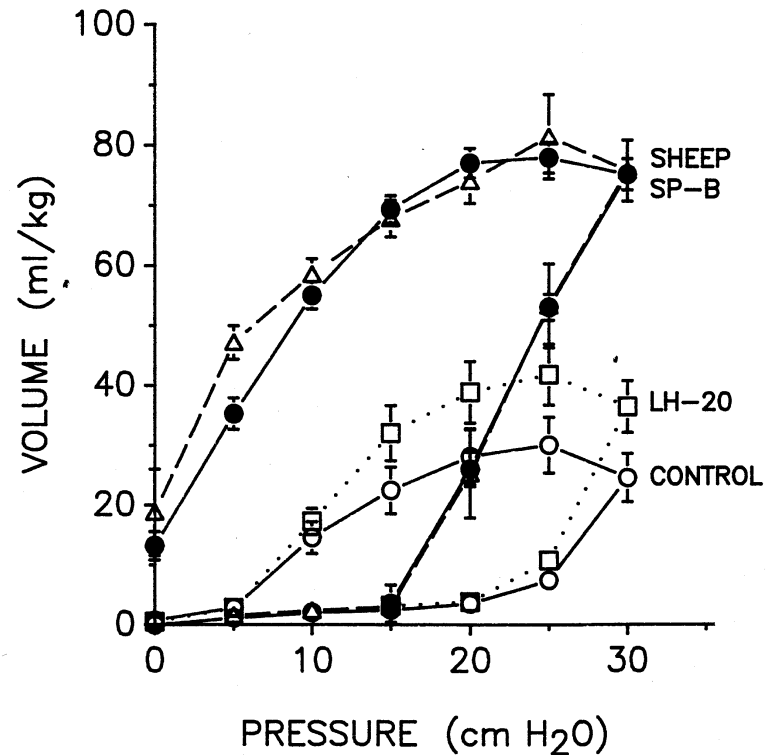
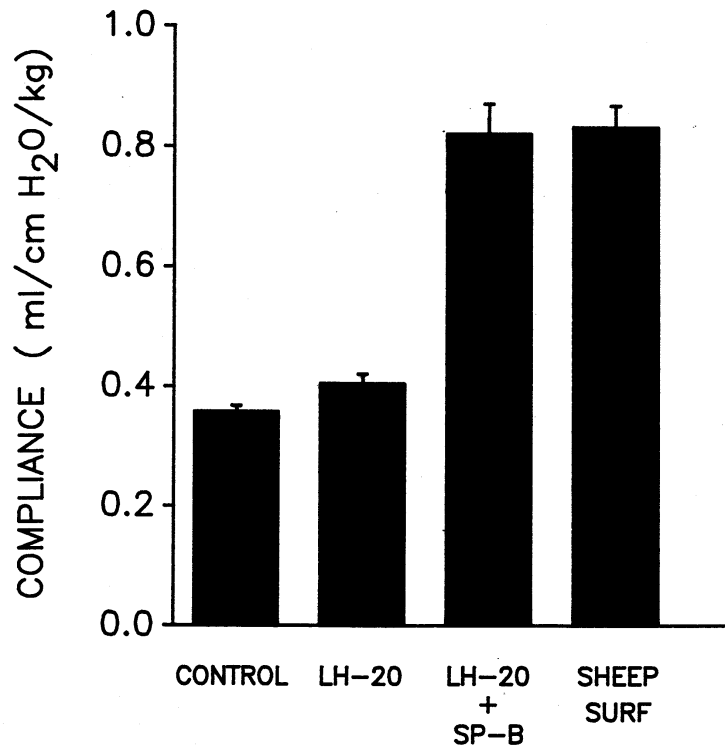
# Surfactant and RDS

- Miracle drug that replaces the primary deficiency.
- A diagnostic agent – clinical responses to treatment test the contribution of surfactant to the respiratory distress.

# Surfactant Effects on Static Pressure-Volume Curves



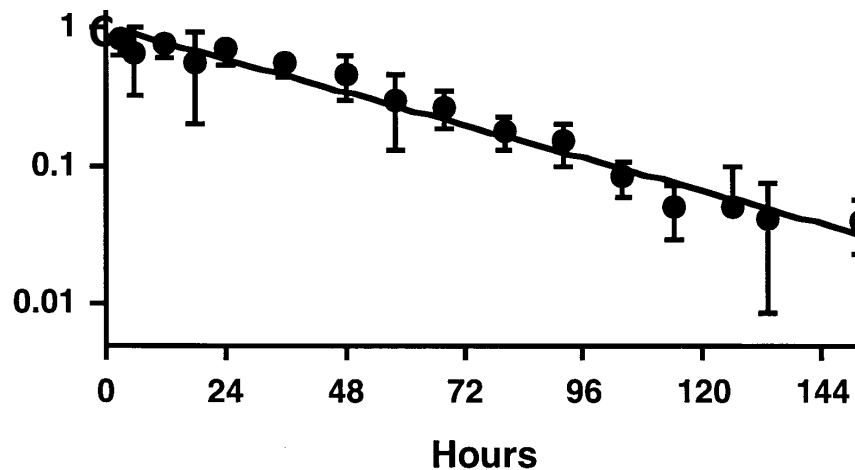
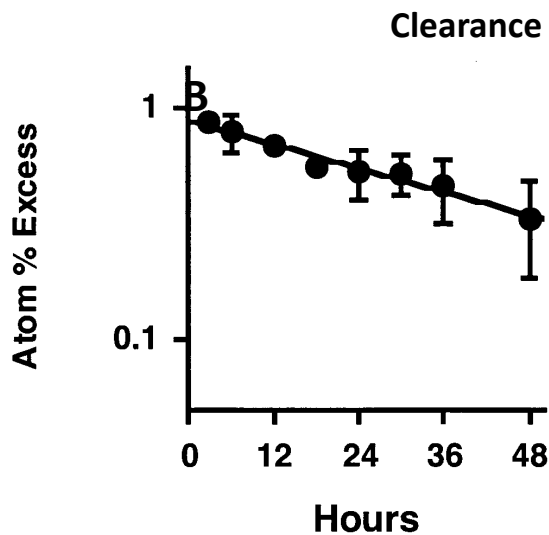
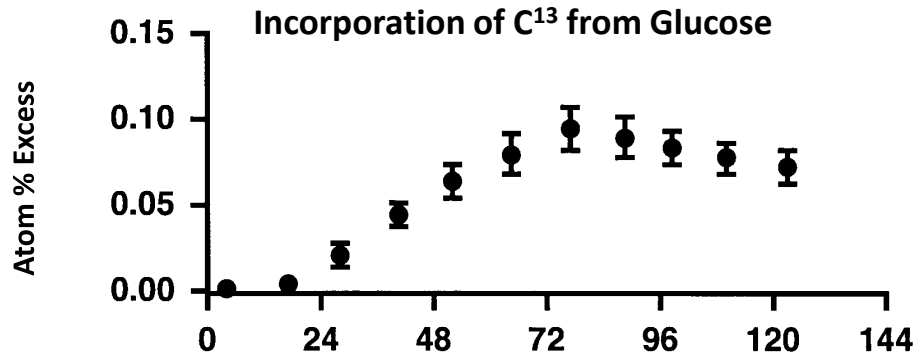
# Effect on SP-B to Surfactant in Ventilated Preterm Rabbits



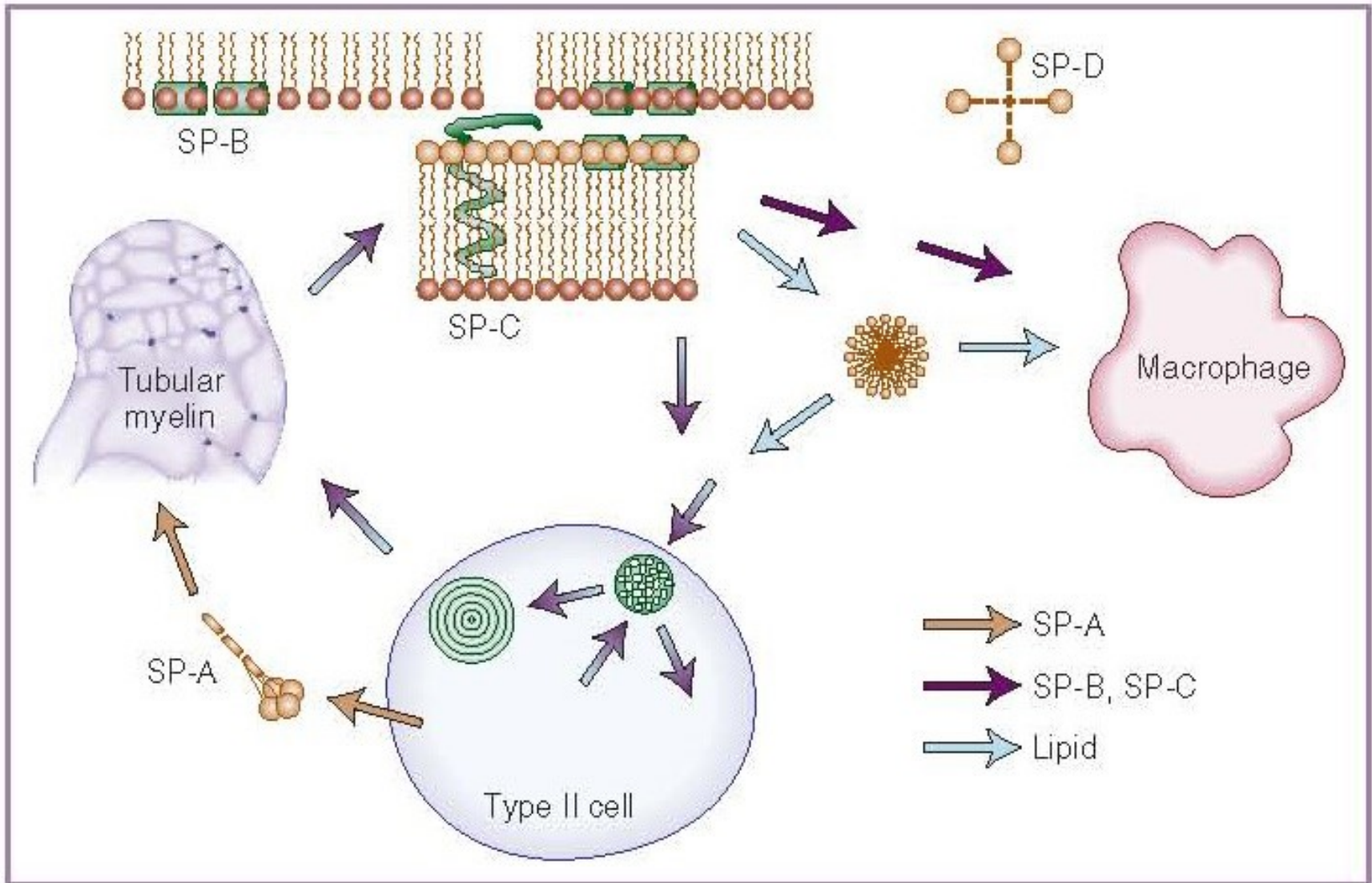
**Surfactant composition matters.**

Rider et al., Am Rev. Resp. Dis., 1993

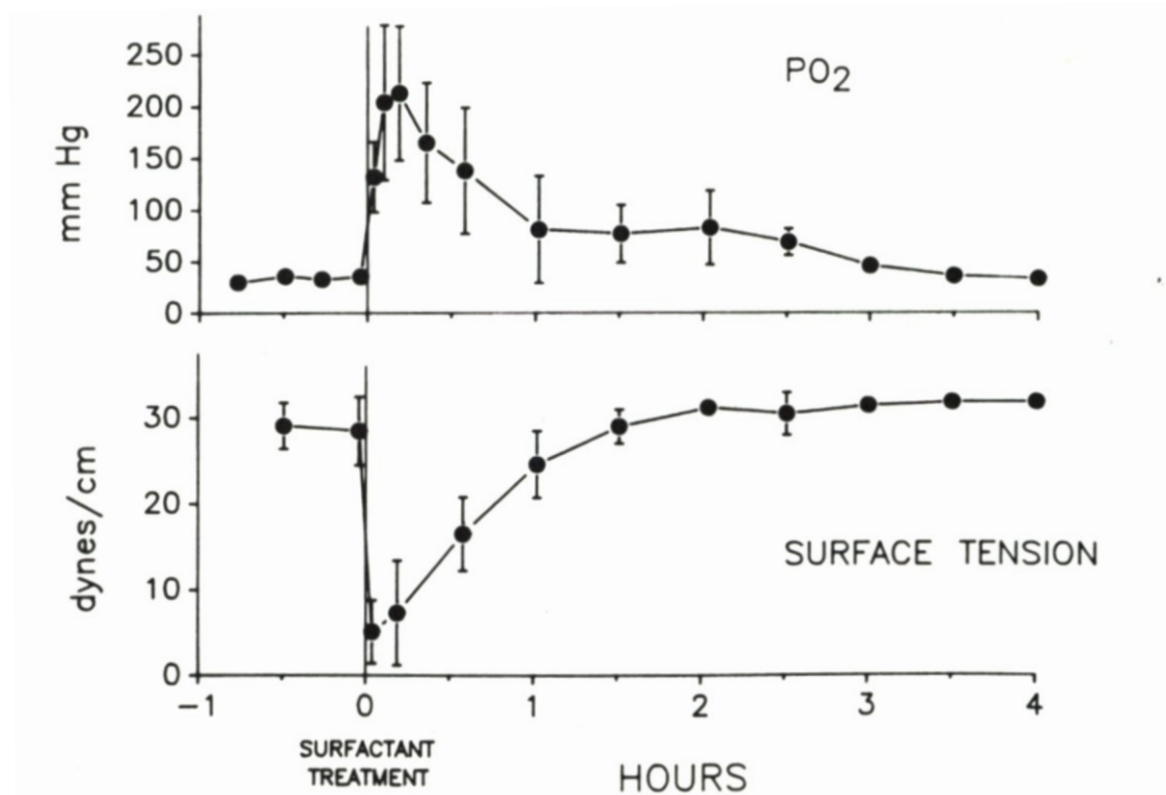
# Labeling of Surfactant Phosphatidylcholine in Airspaces of Infants with RDS



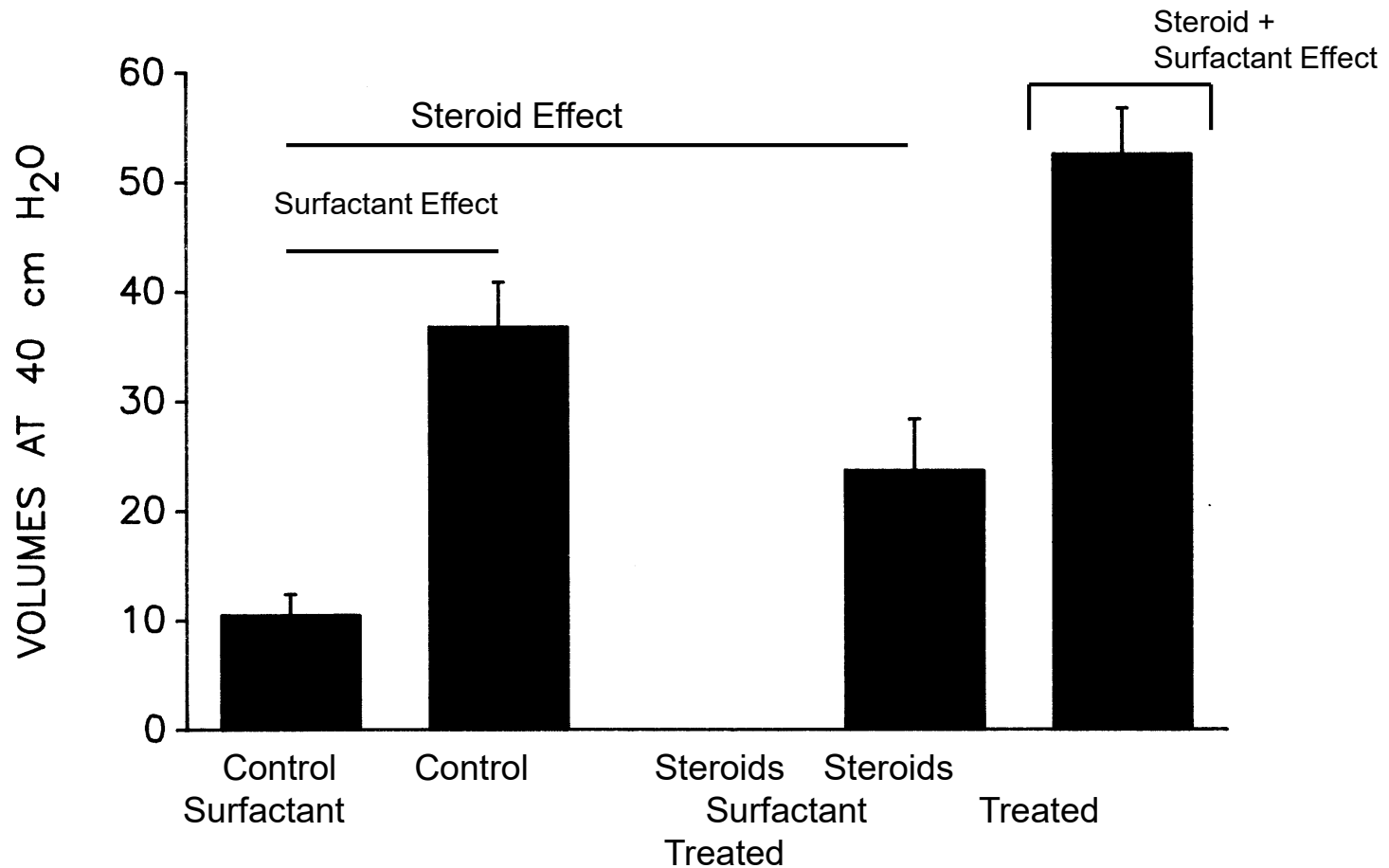
# Alveolar Metabolism of Surfactant



# Effect of Surfactant Treatment on Oxygenation and Surface Tension in Injured Preterm Lamb Lungs



# Effects of Surfactant and Corticosteroid Treatments on Lung Volumes of Ventilated Preterm Lambs



# Surfactant in the surfactant deficient lung

- Surfactant treatments profoundly alter lung function.
- Endogenous surfactant is slowly metabolized and recycled.
- Surfactant function can be degraded by injury / edema.
- Surfactant interacts with antenatal steroids to further improve lung function.

# Antenatal Testing for RDS

- Good tests of lung maturation are no longer available.
  - L/S ratio, PG, Lung Profile, TDX
- Poor tests available, but seldom used.
- Obstetricians deliver infants when “clinically indicated”.

An opportunity: Develop tests to evaluate fetal maturation

# Fetal Amniotic Fluid mRNA

Kamath-Rayne, et al. BMC Med Genom, 2015

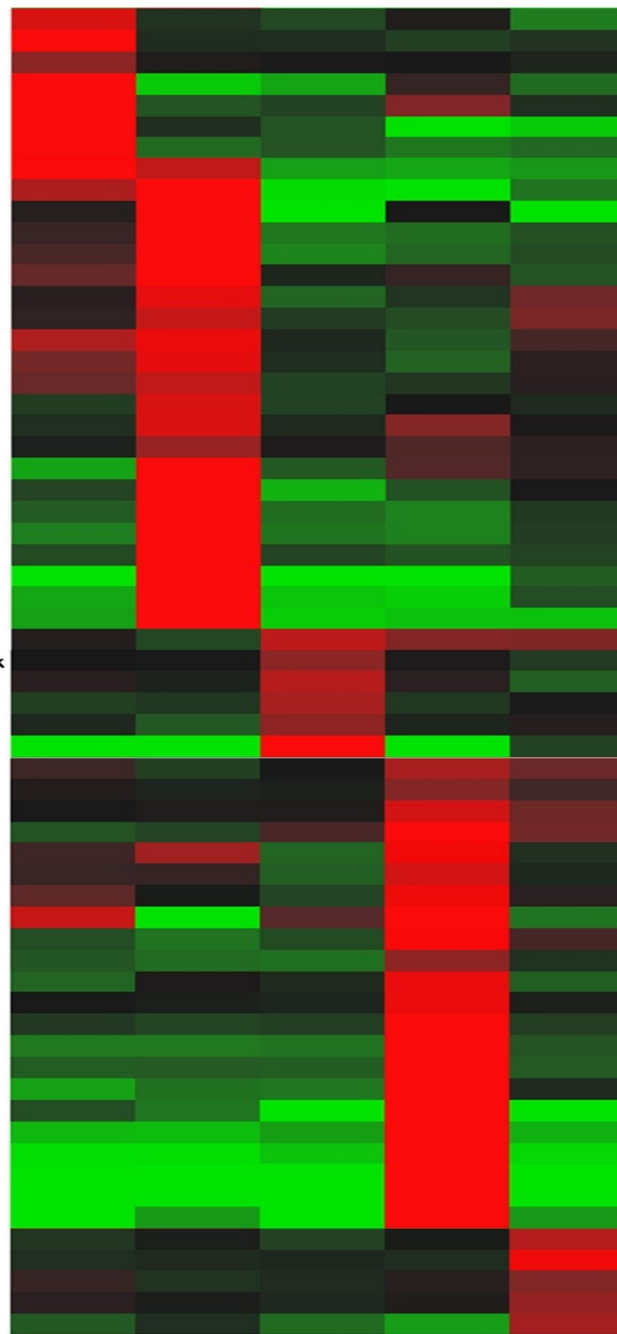
Skin

Lung

Placenta

Bladder

MM9  
Upk2  
Slmap  
Upk1b  
Upk3b  
Sprr1a  
Upk1a  
Lvl  
Ket15  
Pof1b  
S100a14  
Trim29  
Tacstd2  
Dsp  
Tns4  
Gata3  
Perp  
Sfn  
Krt23  
Krt80  
Milt4  
Soel  
Anxa8  
Cst6  
Kprp  
Krt17  
Crct1  
Krt14  
Csta  
Gpx3  
4833439L19Rik  
Albhd14b  
Cndp2  
Tmbim4  
Fxyd2  
Akap2  
Sorbs3  
Epas1  
Clic5  
Emp2  
Hopx  
Hpqcl  
Wfdc2  
Gprc5a  
Lpcat1  
Limch1  
Nckap5  
Rtkn2  
Sogb3a  
Sftpb  
Slc34a2  
Cyp2f2  
Plunc  
Sogb3a2  
Sftpa1  
Sftpc  
Sogb1a1  
Creg1  
Peg10  
Fndc3b  
Rbms2  
Slc2a1



bladder epidermis kidney lung placenta

# Antenatal Influences on Lung Maturation/Development

<b>Diabetes</b>	<b>Delays Maturation</b>
<b>Maternal Smoking</b>	<b>Interferes with Lung Development</b>
<b>Fetal Growth Restriction</b>	<b>Abnormal Lung Development</b>
<b>Corticosteroids</b>	<b>Induced Lung Maturation</b>
<b>Chorioamnionitis</b>	<b>Maturation or Injury</b>

**These factors alter the lung structure and surfactant.**

# **RDS is less frequent now than often appreciated because -**

- Biology of induced lung maturation
  - Antenatal corticosteroids
  - Antenatal exposure to inflammation
- But diagnosis depends on diagnostic criteria.
- But diagnostic criteria are imprecise.

# Diagnosis of RDS for Infants <28 wks. - NICHD Neonatal Research Network

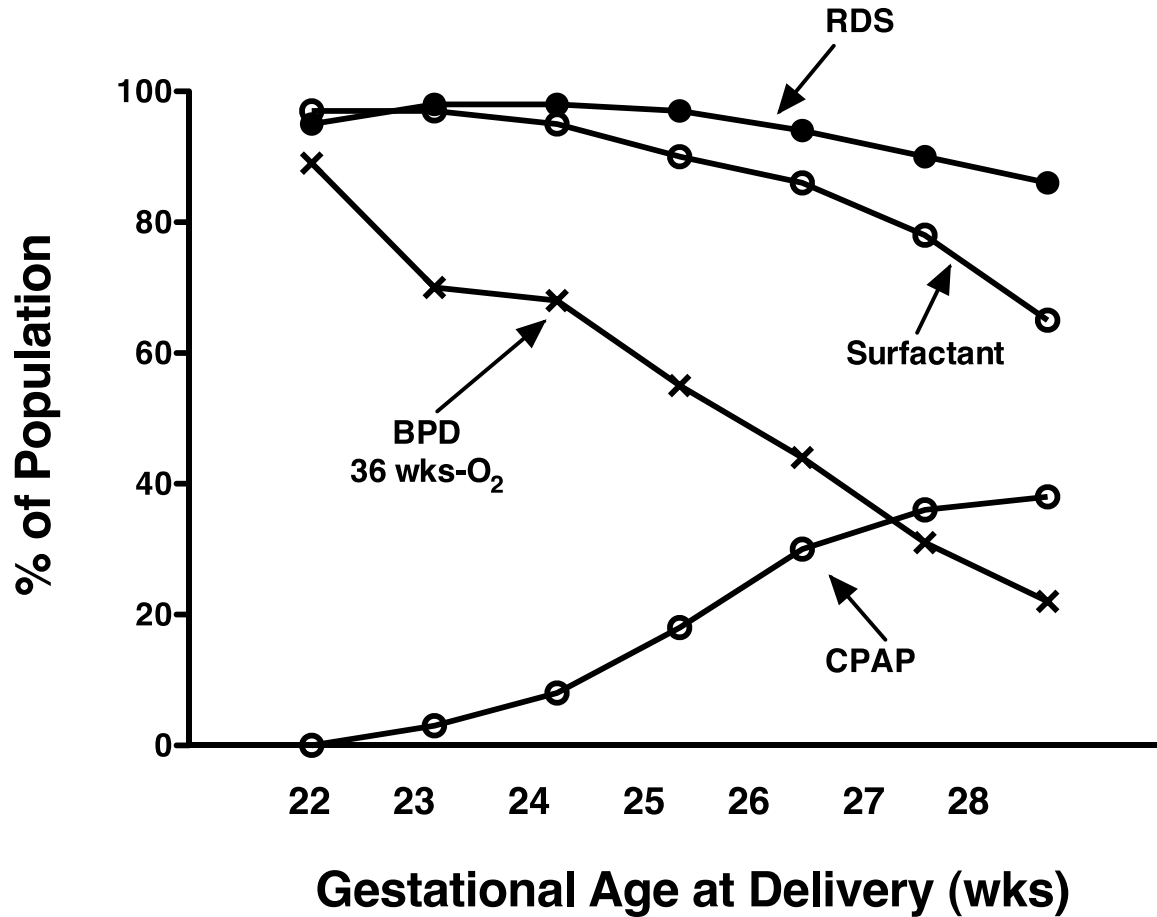
- RDS requires oxygen use from 6-24h of life, respiratory support to 24h, and a chest x-ray consistent with RDS. *1997-2002 (Fanaroff, 2007)*
- RDS requires oxygen use or respiratory support for  $\geq 6$ h only – no requirement for a chest x-ray. *2003-2007 (Stoll, 2010)*

# NICHD – Neonatal Research Network

## Incidence of RDS in VLBW Infants

<b>Study</b>	<b>Infants Reported</b>	<b>% RDS</b>	<b>% Treated with Surfactant</b>
<b>NICHD 1997-2002 (Fanaroff – 2007)</b>	<b>500-1000g</b>	<b>63%</b>	<b>62%</b>
<b>NICHD – 2003-2007 (Stoll, 2010)</b>	<b>22-28 weeks</b>	<b>95%</b>	<b>76%</b>

# RDS, Treatments, and BPD in NICHD - NN Network for Infants Born at 22-28 wks GA 2003 to 2007 (N=9575)

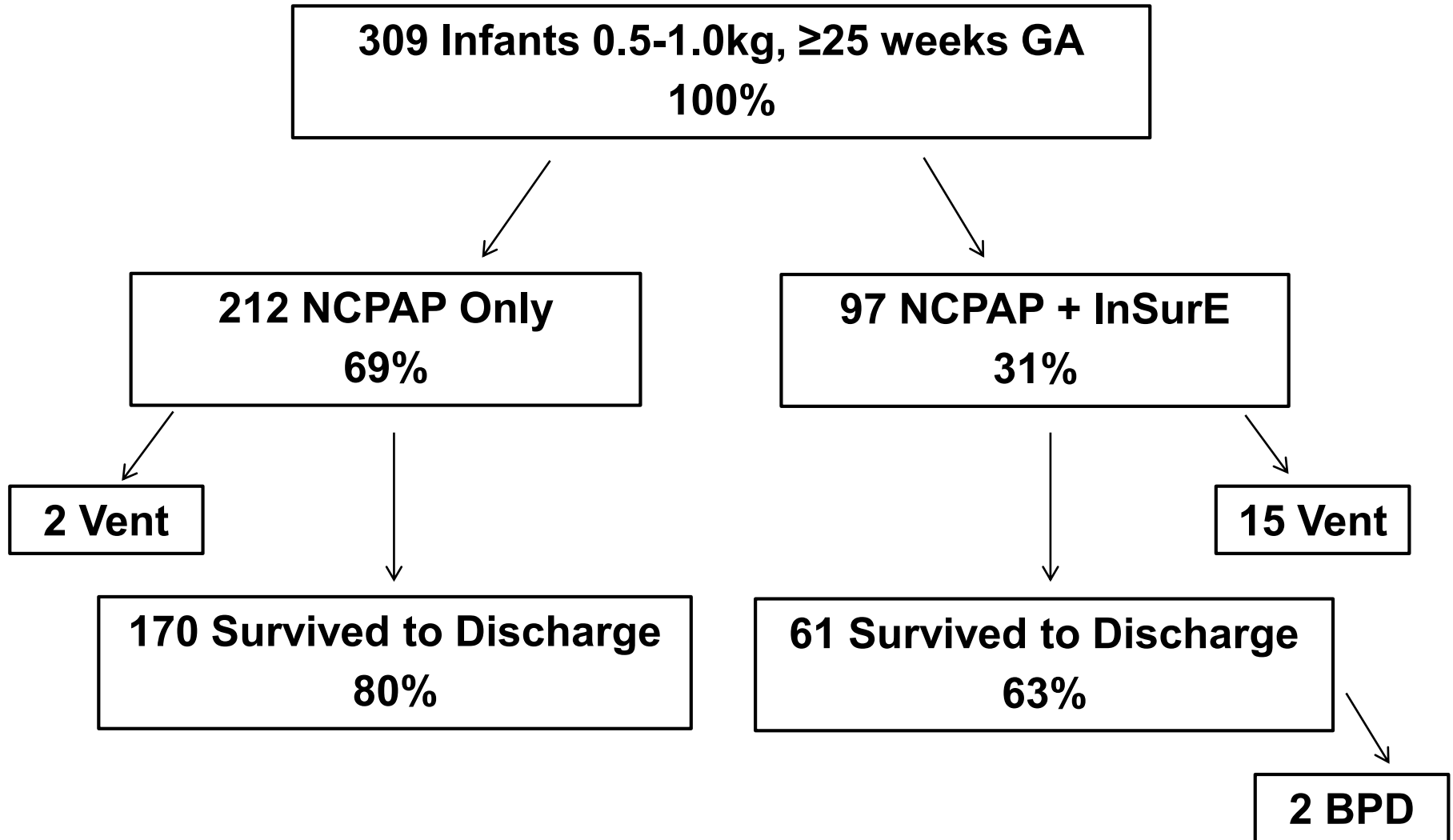


# Incidence of RDS in VLBW Infants

<b>Study</b>	<b>Infants Reported</b>	<b>% RDS</b>	<b>% Treated with Surfactant</b>
<b>Danish Experience - 1999</b>	<b>27 ± 2 weeks</b>	<b>-</b>	<b>30%</b>
<b>COIN Trial</b>	<b>950g average</b>	<b>-</b>	<b>38% (CPAP arm)</b>
<b>NICHD – Support Trial</b>	<b>24-27 weeks</b>	<b>-</b>	<b>67% (CPAP arm)</b>
<b>Vermont-Oxford CPAP Trial</b>	<b>26-29 weeks</b>	<b>-</b>	<b>45% (CPAP arm)</b>

***\*Severe RDS is not the rule in VLBW infants.***

# A South African Experience where Mechanical Ventilation is Limited (BW-870g, GA – 27.9 weeks, 38% of SGA)



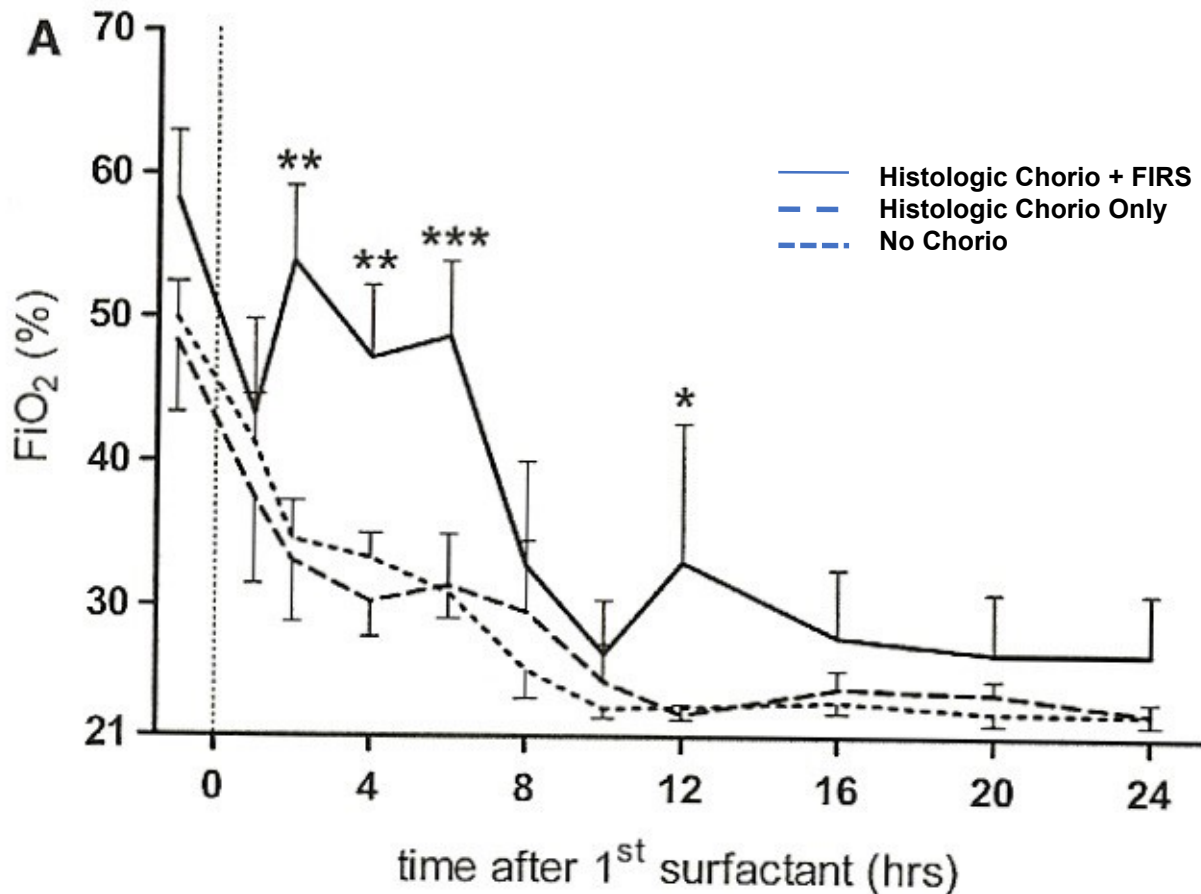
# RDS is less frequent now than often appreciated because -

- Biology of induced lung maturation
  - Antenatal corticosteroids
  - Antenatal exposure to inflammation
- Clinical care strategies
  - Allowing babies to breathe/adapt
  - Using CPAP to transition
  - Recruiting strategies?/Avoiding injury
  - Early surfactant treatments

# Infection/Pneumonia

- 50-70% of infants <32wks GA have been exposed to chorioamnionitis/infection. (*Goldenberg, 2008*)
- About 2% of infants <1kg have a positive blood culture/sepsis at birth. (*Stoll, 2002*)
- The diagnosis of “congenital pneumonia” is seldom made in ELBW infants. (*Stoll, 2010*)
- Tracheal aspirates of these infants have indicators of inflammation/infection. (*Watterberg, 1996; DeDooy, 2003*)

# Oxygenation Responses of Infants with RDS to a Surfactant Treatment



# How can we diagnose lung inflammation/diffuse pneumonia in a ELBW infant if -

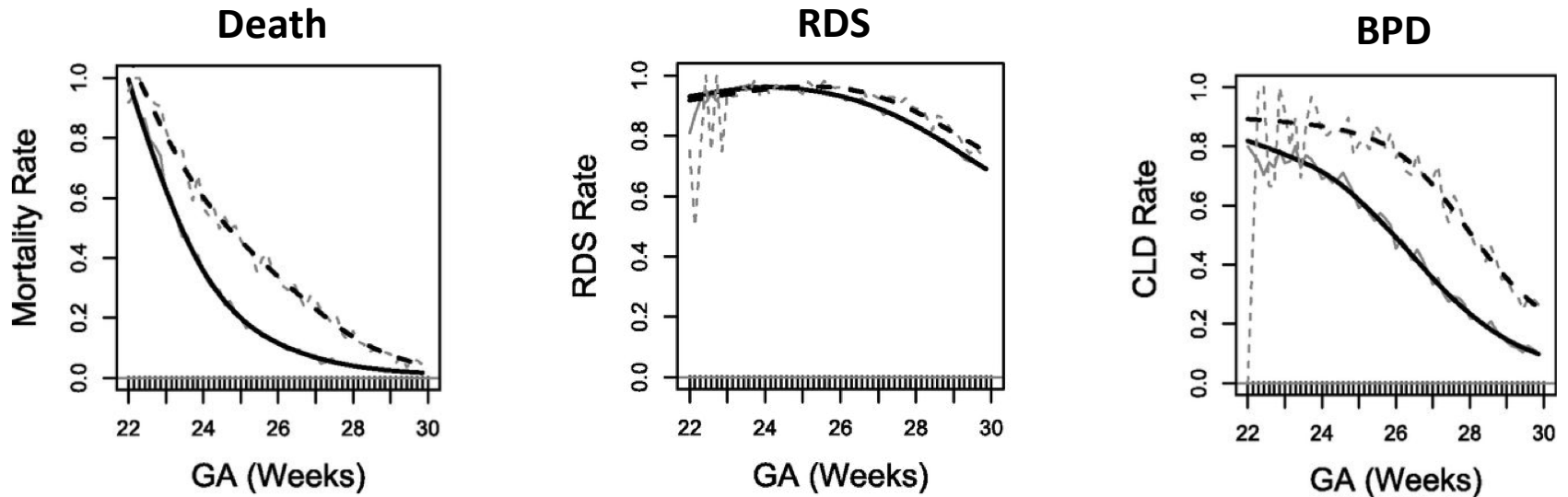
- There is no positive blood culture.
- The organisms are not traditional pathogens (Ureaplasma) or are not culturable.
- The chest x-ray looks like RDS.
- Inflammation/edema inhibits surfactant causing a secondary surfactant deficiency.

# Pulmonary hypoplasia/delayed lung maturation

- Difficult to diagnose in preterm
- No decrease in RDS for SGA infants
- Animal models indicate adverse effects on lung growth from -
  - Growth restriction
  - Maternal tobacco exposure

# Outcomes for 157,000 22-29 weeks GA infants in Vermont – Oxford 2006-2014

---- SGA < 10%    ——— Non SGA



# Confounding effects of delivery room treatments on RDS

**Injury with Mechanical Ventilation**



**Epithelial Leaks and  
Inflammation**



**Surfactant Inhibition**



**“ARDS”**

**Use of CPAP**



**Recruitment of FRC/  
Surfactant Secretion**

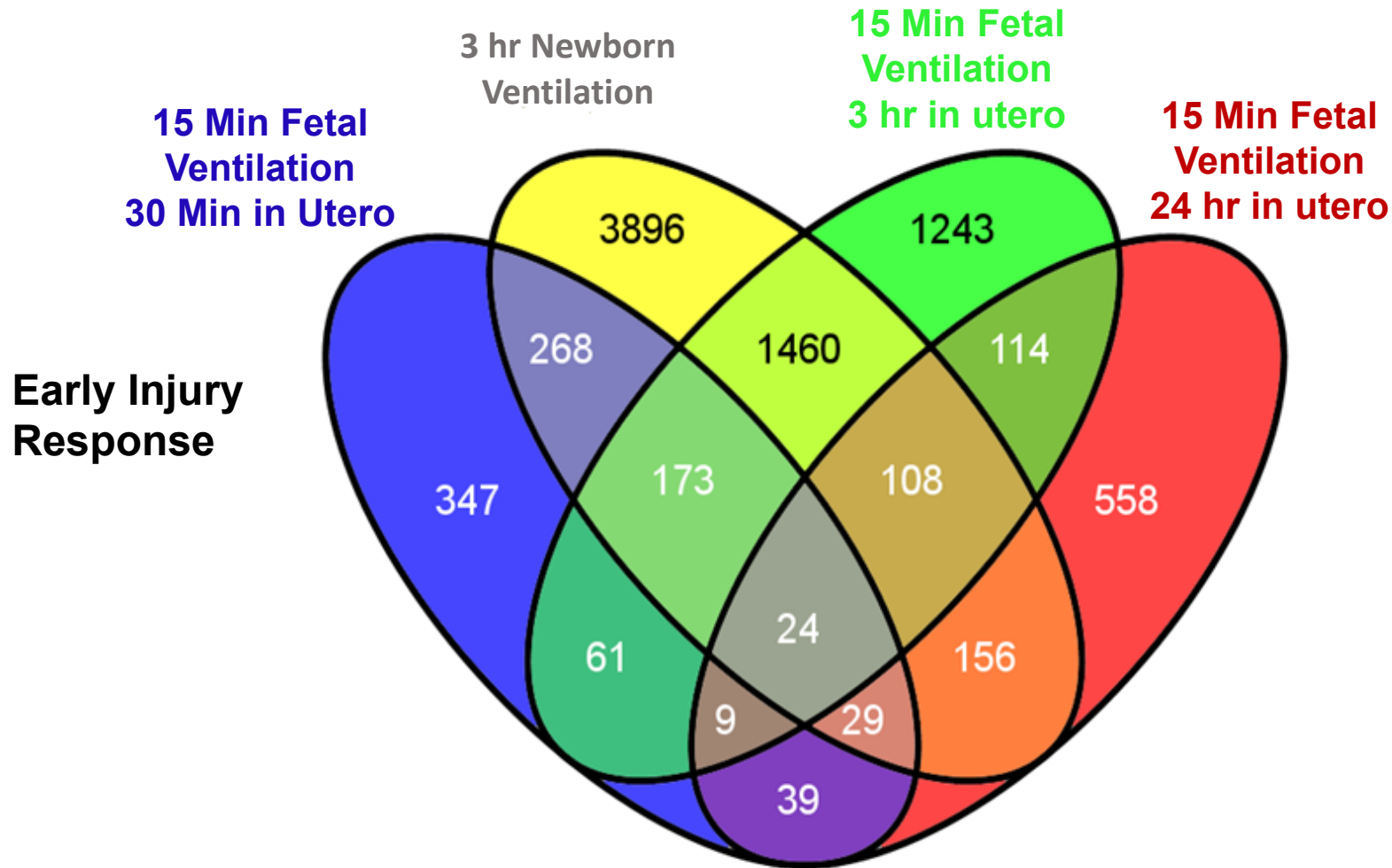


**Minimizing Lung Injury**



**No RDS if Enough Surfactant**

# Differential Regulation of Genes over Time (mRNA Sequencing analysis)



All animals ventilated to 15 mL/kg by 15 minutes and compared to unventilated controls.

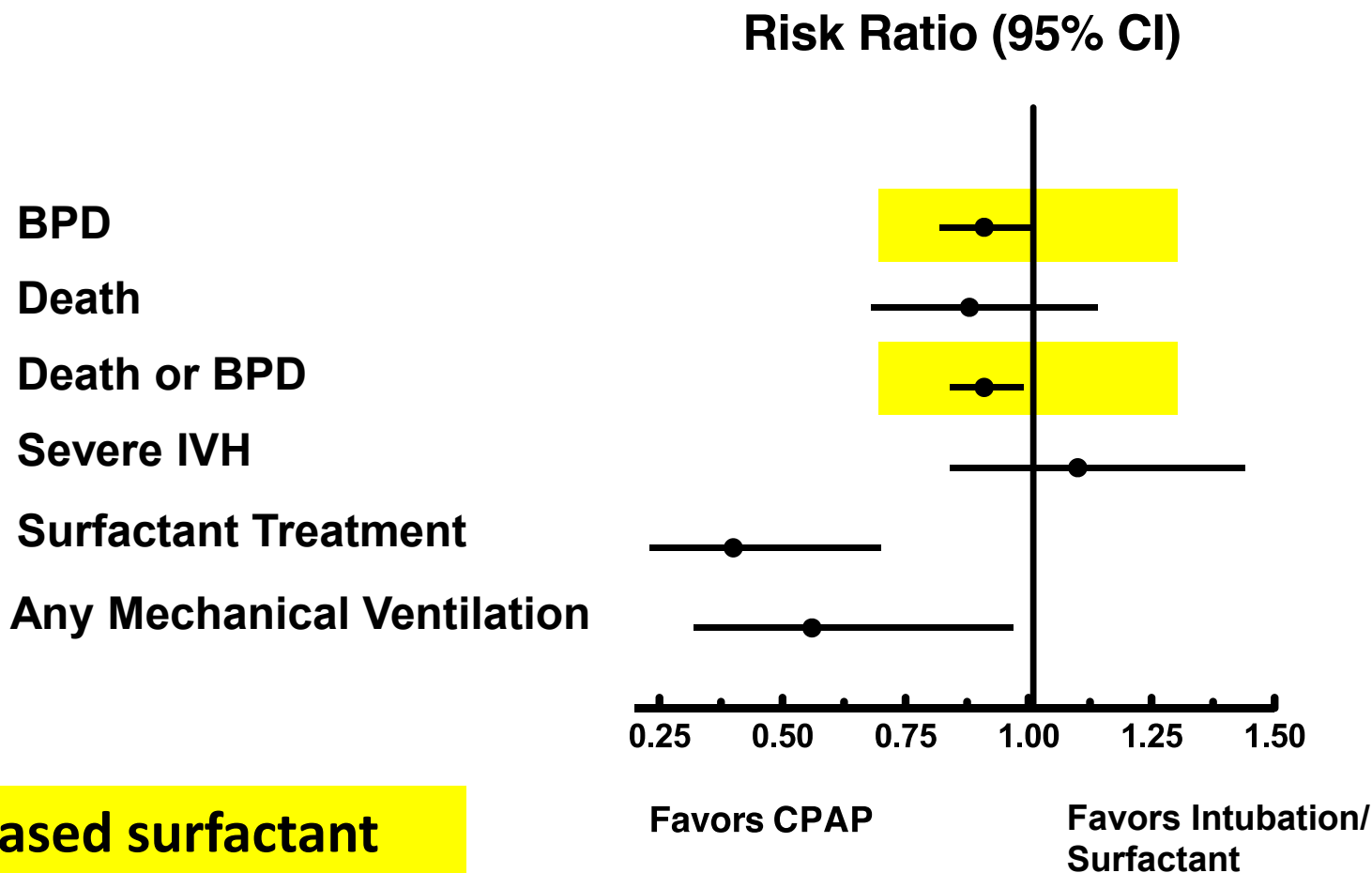
# Early - Delivery room/within 15 min. Surfactant Treatments -

- Do not know who would have had RDS
  - Persistent respiratory distress – is that surfactant deficiency disease?
  - No RDS after treatment – did treatment correct deficiency or was there no deficiency?

# Clinical Trials

- **Can we decrease lung injury by gentle resuscitation (CPAP)?**
- **Does CPAP decrease the diagnosis of RDS?**

# Meta-analysis of 4 Trials Including 2,700 Infants Randomized to CPAP or Intubation and Surfactant Treatments at Birth



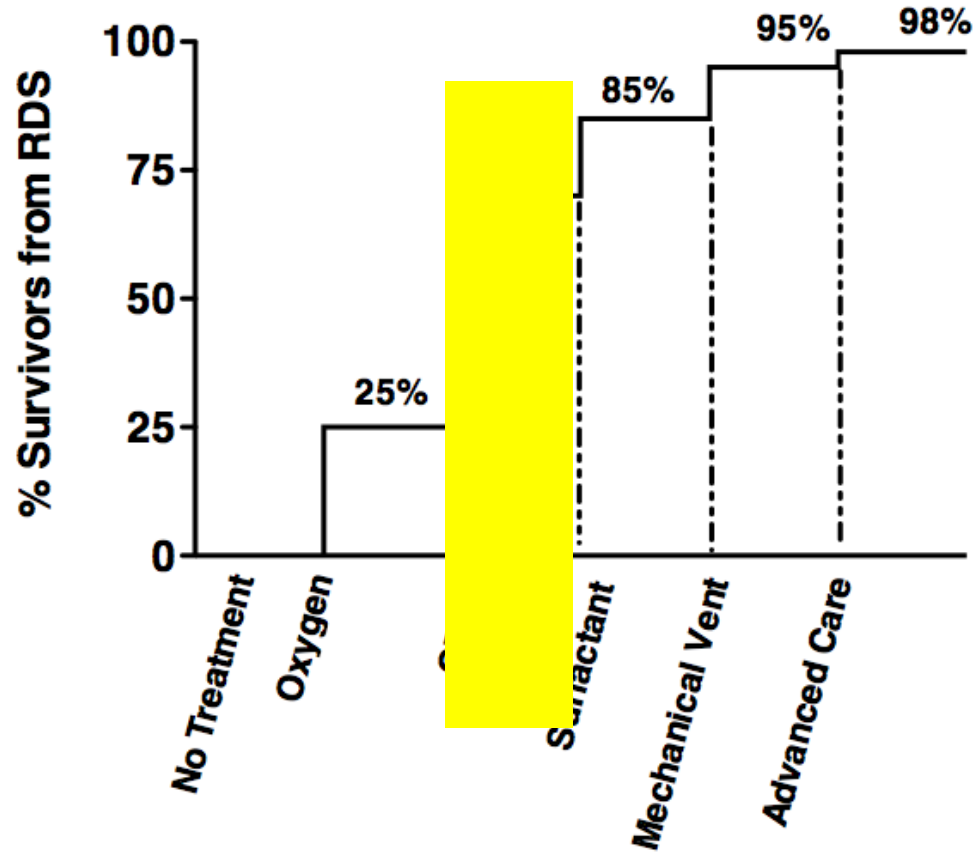
**Decreased surfactant  
does not mean less RDS**

# New “Prevention” Strategies for RDS

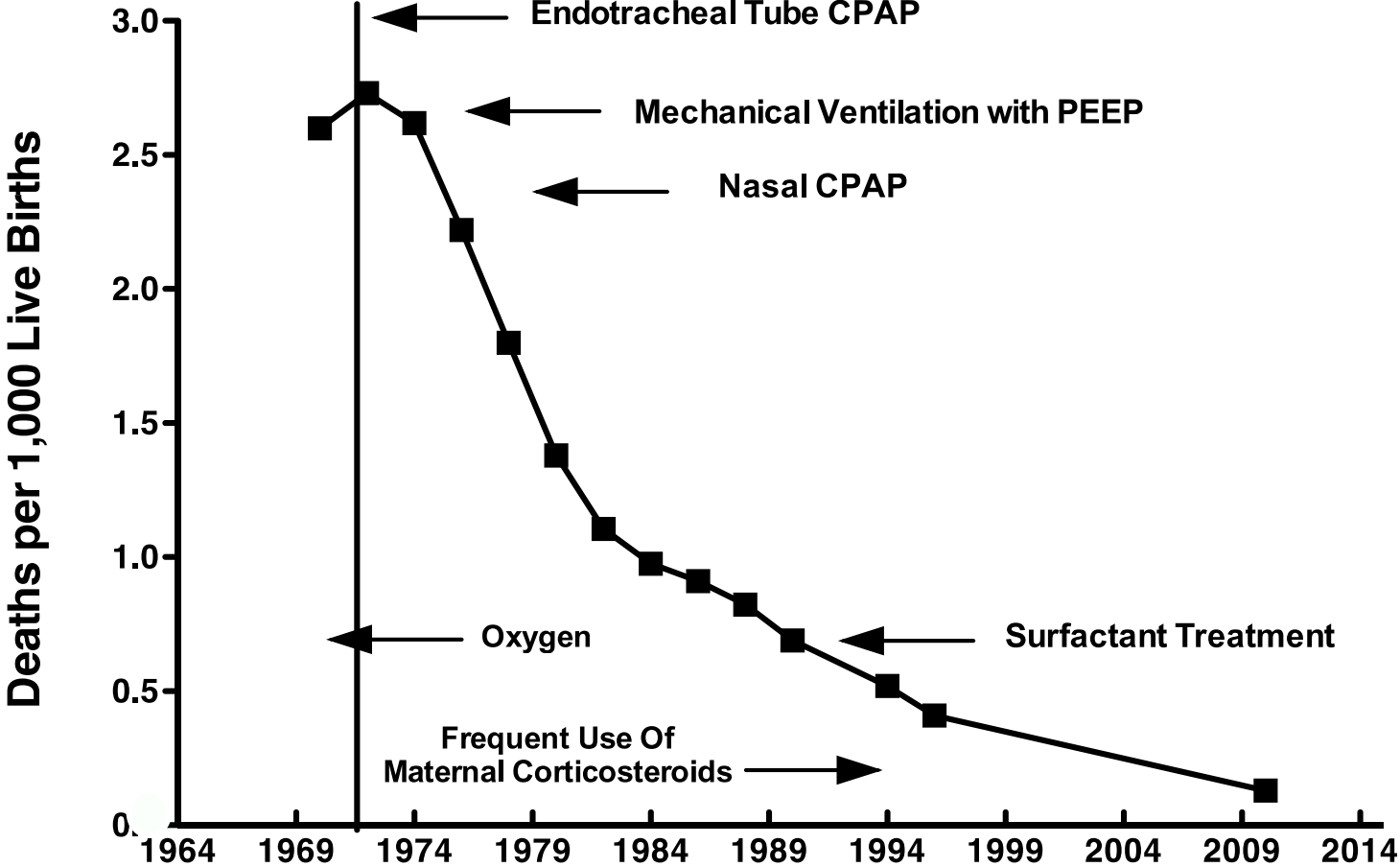
- Antenatal
  - Better drugs/dosing for ANS.
  - New antenatal tests of fetal maturation.
- Postnatal
  - Improved early surfactant treatment techniques.
  - Better surfactants?
  - Better ventilation / respiratory support?

**Infants should not die of  
RDS in 2018**

# Estimated Effect of Introduction of Each Therapy on Survival of Infants with Birth Weights >1.2 kg in Resource Poor Environments



# Mortality from RDS – US Population Data

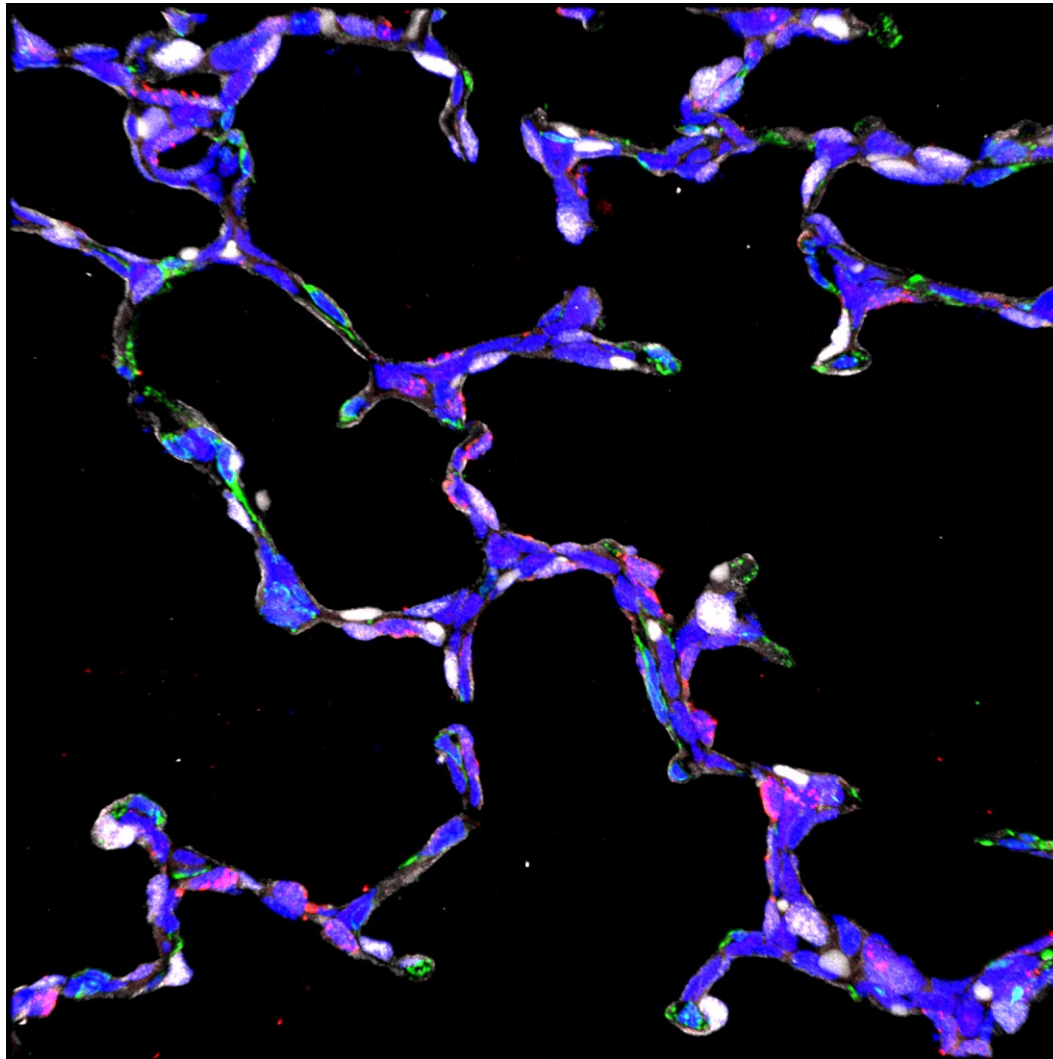


# What is RDS in 2018?

- A disease that seldom is the primary cause of death at GA >28 weeks.
  - Antenatal corticosteroids
- Can be decreased by delivery room management.
- Can be effectively treated with surfactant.

**But: A specific diagnosis is difficult to make.**

# Alveolar Septa: 130d GA (79% Term) Preterm Rhesus



LungMAP