

Breakout Session #2: Neonatal Lung Injury

Robin Steinhorn and Mary Short, Moderators

International Neonatal Consortium



Participants of Neonatal Lung Injury Breakout

**ROBIN STEINHORN &
MARY SHORT, MODERATORS**

- ▶ WOLFGANG GÖPEL
- ▶ ANNE GREENOUGH
- ▶ MAREK MIGDAL
- ▶ HIDE NAKAMURA
- ▶ CECILE OLLIVIER
- ▶ THORSTEN OLSKI
- ▶ DOBROMIR PENKOV
- ▶ BRIAN SMITH
- ▶ STEPHEN SPIELBERG
- ▶ MARTHA BRUMFIELD, C-Path

By WebEx

- ▶ VALENTINE COMITO
- ▶ LISA BETH FERSTENBERG
- ▶ ROSEMARY HIGGINS
- ▶ SATOSHI KUSUDA
- ▶ MARY PURUCKER
- ▶ ANNE ZAJICEK

Neonatal Lung Injury Breakout Session Summary

- ▶ BPD was the prioritized indication from the Neonatal Lung Injury Breakout group
 - ▶ High incidence
 - ▶ Significant morbidity
 - ▶ High Resource Utilization
 - ▶ Research focus should be prevention- could preventing BPD decrease other neonatal morbidities being prioritized (sepsis, ROP, NEC)
- ▶ Feasibility
 - ▶ Challenges related to biomarker, SOC, clinical endpoints but this is balanced with
 - soon to be released PROP study including biospecimens
 - Available “captive” population
 - Extensive data collection on this population
 - German Neonatal Network genomics data base

BPD was also a priority in the pre-consortium survey

Response to Breakout Question #1

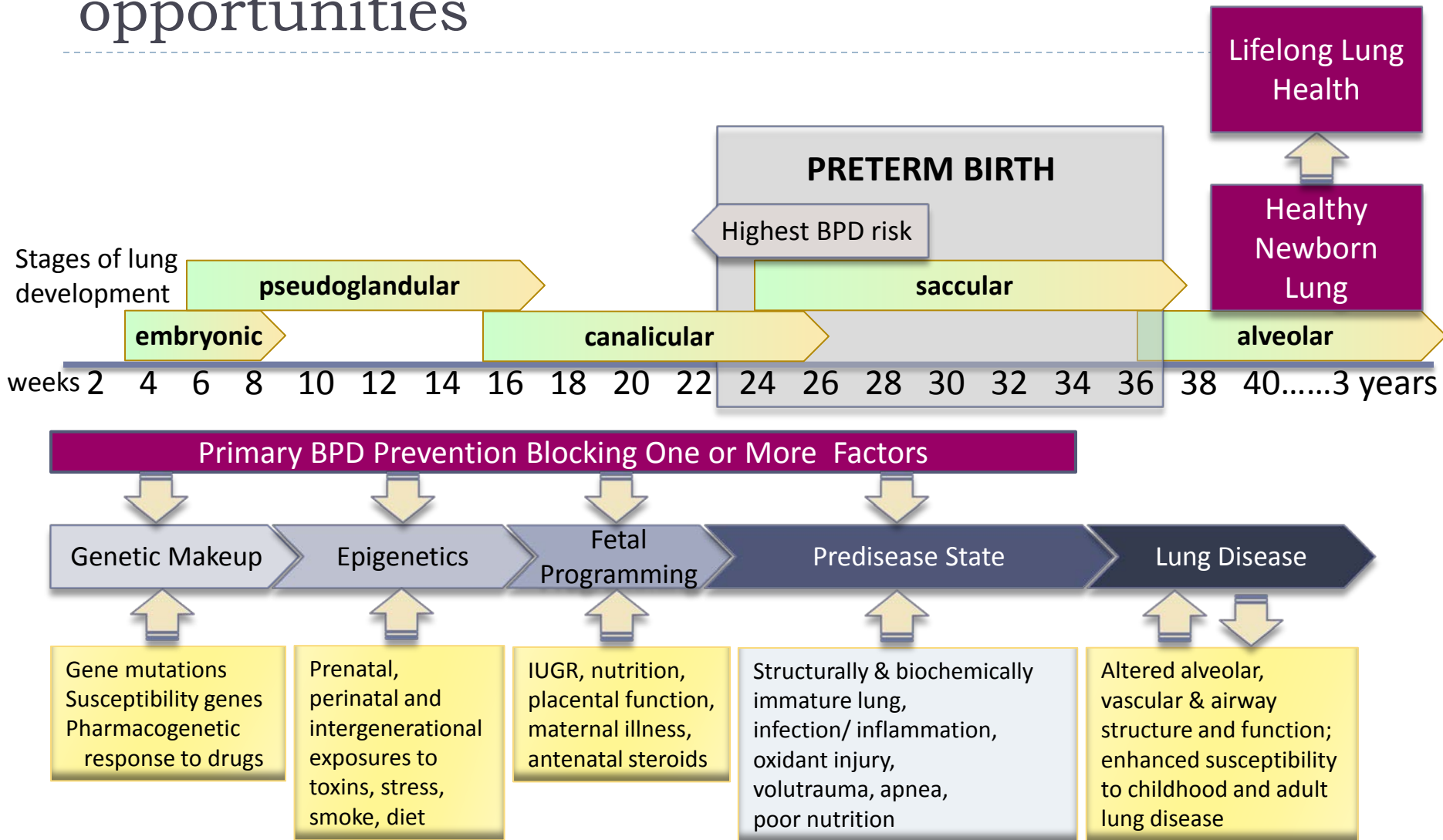
- ▶ For neonatal lung injury, what indication(s) are in most need of effective therapies?
 - ▶ **Bronchopulmonary Dysplasia- *redefine – focus on prevention***
- ▶ Include an estimate of the incidence and severity.
 - ▶ Most common complication of preterm birth ¹
 - ▶ 30-60% of infants < 29 weeks PMA and weighing $\leq 1250\text{g}$
 - ▶ The incidence of BPD is rising with increasing survival of LBW infants (< 1000 g)
- ▶ Effects last into adolescence and adulthood
- ▶ Few effective, evidence-based therapies
- ▶ Preventing BPD would solve many other morbidities of prematurity, including long term neurodevelopmental impairment

Challenges to BPD Prevention Research

- ▶ BPD – complex phenotypes (BPD in a 25 week infant is probably a different disease than that in a 29 week infant)
- ▶ Multi-institutional collaborations essential, but introduce variability in practice and outcomes
- ▶ Current challenges in balancing risks and benefits of preventive strategies
 - ▶ Some premature infants not destined to develop disease will be exposed to experimental therapies with potential adverse effects
 - ▶ Adverse effects may not be evident for months or years



Primary prevention for BPD: Windows of opportunities



Improving feasibility of BPD Prevention

- ▶ Identification of genomic therapeutic targets is now feasible
- ▶ PROP (Pediatric Respiratory Outcomes of Prematurity)
 - ▶ NHLBI-sponsored consortium, enrolled 765 ELBW preterm infants across 6 centers
 - ▶ All with deep phenotyping through 1 year of age and biorepository samples
- ▶ Other functional networks and data warehouses now well established (eg, NICHD Neonatal Research Network, German Neonatal Network)



Response to Breakout Question #2

- ▶ For indication X, what non-clinical studies need to be carried out prior to designing clinical trials of new and/or existing drugs?
 - ▶ Are animal models available for the indication (e.g. gestational age equivalent)?

Multiple animal models exist, although none are perfect:

Preterm sheep

Preterm baboons

Neonatal mice, rats

- ▶ Can the non-clinical data be extrapolated to inform clinical development, including initial dosing?

Probably yes. There is a need for :

- ▶ Non –animal models simulating lung development
 - ▶ Modelling with fetal/neonatal lung explants

Response to Breakout Question #3

- ▶ For indication X, what information would be needed before starting a clinical trial?
 - ▶ Can existing pediatric or adult studies be extrapolated to neonates?

Extrapolation of data to very young pediatric patients, particularly neonates, is rarely credible. (FDA Guidance on Clinical Pharmacology 2014)
 - ▶ Would the use of different drug classes alter the inclusion/exclusion criteria?
 - ▶ Frequently this is the case.
 - ▶ Eligibility criteria is usually dependent on class of drugs and phase of study development
 - ▶ Maybe. Some agents are likely to be used at birth, others later when infant might be at higher risk (on vent at 21 days)
 - ▶ Do the inclusion criteria drive formulation, mode of administration and/or dose?
 - ▶ Inclusion criteria determines study population which could dictate mode of administration as well as appropriate formulation
 - ▶ Some agents are likely to be used at birth, others later when infant might be at higher risk (on vent at day 21).
 - ▶ No, those elements are dependent on the pharmacology of the drug.
 - ▶ What parameters are needed for constructing a meaningful modelling and simulation tool?
 - ▶ Very specific and standard definitions of variables, how to measure them, and what endpoints and outcomes are being studied.

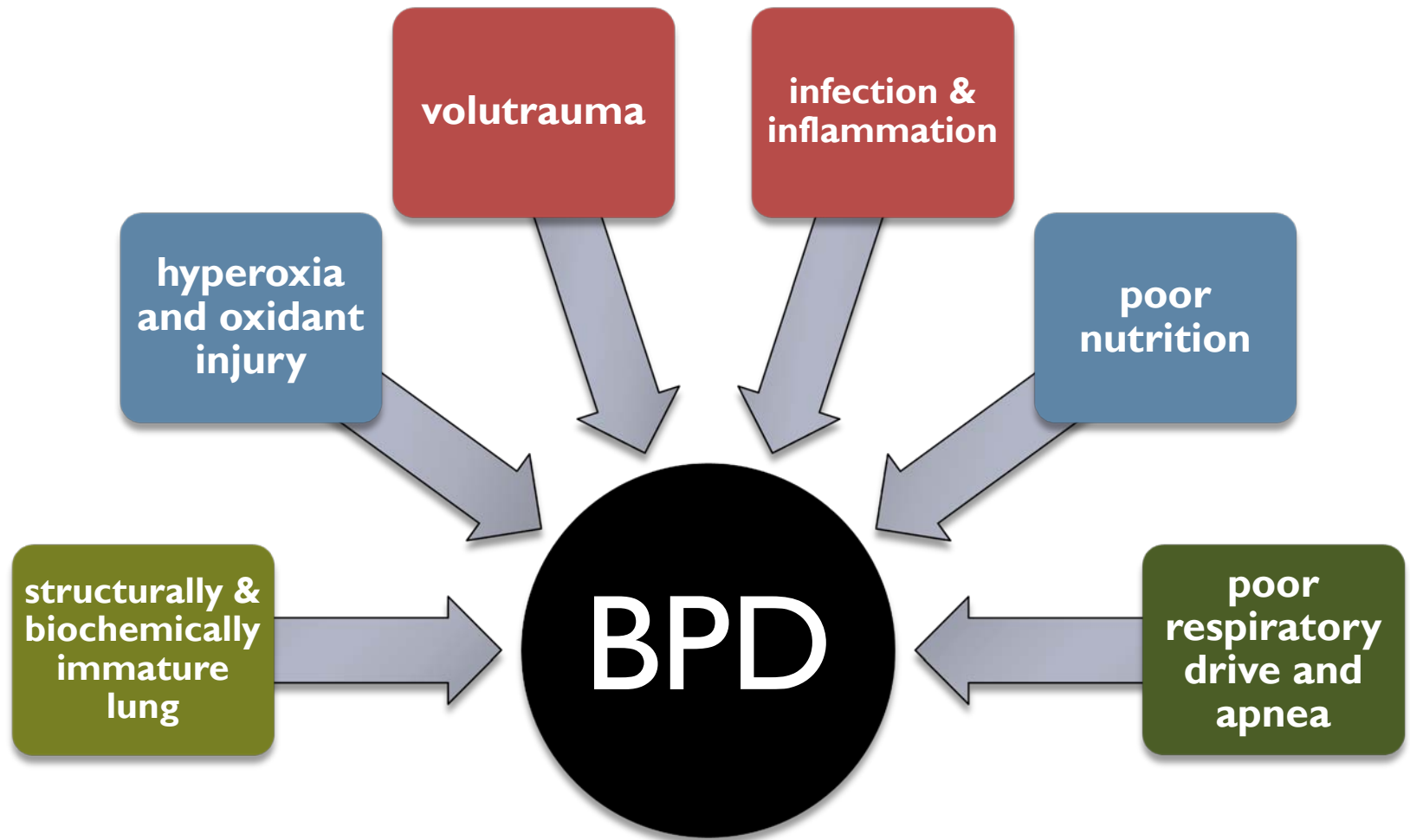
Response to Breakout Question #4

- ▶ Are there impediments to establishing a master protocol (do multiple approaches exist – comparative effectiveness studies)?
 - ▶ Extremely difficult to do
 - ▶ Hard to blind given that the different therapies would likely be dosed differently (inhaled, IV, PO) and at different ages, but it would give you a group to compare new therapies in the protocol to.
 - ▶ Learn from oncology community (example, COG protocols)
 - ▶ Master Protocol approach considered for adolescents with T2DM – discuss the challenges
 - ▶ Interoperability of the data collection systems would be important to capture.
 - ▶ Patient-level data is a must as well as the accepted standard of care the neonate
 - ▶ IRBs are one impediment as there is a wide range of comfort levels .
 - ▶ Technological capabilities may not be uniform across different NICUs.
- ▶ Is there equipoise?
 - ▶ Should be equipoise since no other therapies work

Response to Breakout Question #5

- ▶ What potential biomarkers and clinical trial endpoints could be used?
 - ▶ Are adequate clinical outcome measures available? If not can they be developed?
 - ▶ Most studies would need to incorporate death as competing outcome and NDI as either primary or important secondary
 - ▶ **PROP biospecimens data bank- deep phenotyping, improved definitions, and genomics from biorepository are likely to yield new biomarkers**
 - ▶ **German Neonatal Network – genomics**
 - ▶ Earlier biomarkers, dynamic biomarker
 - ▶ Noninvasive transthoracic echocardiography markers
 - ▶ Other dynamic BPD risk indicators (ie, change from day 7 to day 28)
 - ▶ Benchmarking Study data
 - ▶ Data mining for clinical trial endpoints

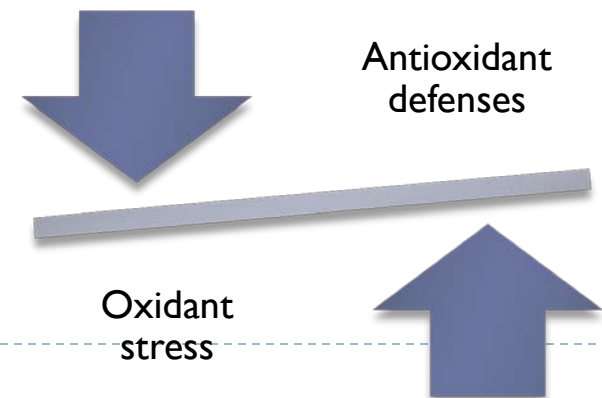
Abnormal pulmonary development associated with BPD



Responses of individual patients modulated by genetic, epigenetic and antenatal factors

Challenges of Biomarker Research for BPD

- ▶ Appropriate control group
- ▶ Multiple confounders
- ▶ Absolute value versus change over time
 - ▶ Continuous variable, cutoff or quartiles?
- ▶ Interactions among various biomarkers
 - ▶ Balance of inflammatory and anti-inflammatory cytokines; angiogenic factors, pro- and antioxidants; alpha and gamma tocopherol



Response to Breakout Question #6

- ▶ What long-term outcome measures are available to assess the safety and efficacy of the therapy?
 - ▶ 18-22 month Bayley is standard for survival without NDI endpoint (but consider new measures such as “gain of milestones”)
 - ▶ Efficacy measures: time on ventilator, length of hospitalization, O2 at discharge, BPD
 - ▶ Number of doctor visits for respiratory symptoms and events
 - ▶ Hospitalizations for respiratory symptoms and events
 - ▶ Safety measures: ROP, NEC, sepsis, IVH, etc.
 - ▶ Potential for examining longer term measures -- respiratory function at age 5-6 years, adolescence, adulthood

Response to Breakout Question #7

- ▶ In light of your responses to Questions 1-6, where are the gaps in knowledge and how would you prioritize the studies needed to approach the neonatal lung injury indication?
 - ▶ Genomics and other 'omics' to identify novel drug targets
 - ▶ Standardize the definitions used to describe symptoms, variables and outcomes
 - ▶ Harmonize EDW between countries for data mining
 - ▶ Biomarker development
 - ▶ Off patent use of pharmaceuticals – correct dosing of dexamethasone, diuretics (loop), hydrocortisone, etc (use techniques similar to those presented for Pediatrix EDW)

DETAILED RESPONSES

Response to Breakout Question #1

- ▶ For neonatal lung injury, what indication(s) are in most need of effective therapies?
 - ▶ Bronchopulmonary Dysplasia with Pulmonary Hypertension
- ▶ Include an estimate of the incidence and severity.
 - ▶ Incidence of 18%–25% of preterm infants,⁷⁹⁻⁸¹ and is associated with high mortality (30%–40%), especially if sustained beyond the first months of life.⁸²⁻⁸⁵
 - ▶ BPD occurs in 8% to 25% of preterm infants, and 40% of infants with BPD also have pulmonary arterial hypertension (PAH). Unfortunately, infants with BPD related to PAH have a high mortality rate of 14% to 50%.¹⁻
 - ▶ Incidence of BPD associated late PH (8%) in that study was lower than previous reports, which range as high as 43%¹¹ and ¹³; however, these reports may be subject to selection bias because of their retrospective study design and enrollment of infants with severe respiratory disease who were referred for evaluation of PH. The reported median age for the diagnosis of BPD and PH is 4.5 months (IQR 2.4-7.8 months).²⁶
 - ▶ up to 10% of extremely low birth weight infants have PH at hospital discharge; however, all infants with BPD were not screened for PH at 36 weeks' PMA or later.
 - ▶ Kim et al³⁰ prospectively screened 98 infants with moderate or severe BPD and reported a 25% incidence of BPD associated PH. 7% of infants with moderate BPD and 52% with severe BPD had PH.
 - ▶ up to one-third of premature infants recovering from RDS had echocardiographic evidence of persistently elevated PAP even if breathing room air at hospital discharge

Response to Breakout Question #2

- ▶ BPD, what non-clinical studies need to be carried out prior to designing clinical trials of new and/or existing drugs?

- ▶ What juvenile animal toxicity studies are needed?

ICH M3 guideline: nonclinical studies that support initiation of pediatric trials typically include core safety pharmacology studies (cardiovascular, CNS, respiratory), repeat-dose toxicity studies, a genotoxicity battery, fertility studies and pre- and postnatal development studies.

Juvenile toxicity studies are conducted on a case-by-case basis

Small molecules: the rat is generally the species employed. Feasibility is an important consideration: e.g., the youngest age at which rats can be dosed by oral gavage is about 4 days of age, which roughly corresponds to just before birth for humans; about 10 days of age roughly corresponds to the human term neonate.

Large molecules for which monkey may be the only appropriate species due to immunogenicity issues with rodents pose additional challenges. Infant monkeys cannot be shipped without their mothers until 6-12 months of age, which roughly corresponds to a human infant/toddler – this misses the time window of a pre-term or term human. For this case, an enhance pre- and postnatal development study would be appropriate in which the mother is dosed up to delivery and then assessment are performed on neonates and infants.

Response to Breakout Question #2

- ▶ For indication X, what non-clinical studies need to be carried out prior to designing clinical trials of new and/or existing drugs?
 - ▶ Can the non-clinical data be extrapolated to inform clinical development, including initial dosing?

An assumption for the starting dose would be dependent on whether the exposure demonstrates and effect on the biomarker or outcome of interest. Allometric scaling is the usual method that takes into account the size of the animal used in the model to the paediatric patient. However, it can be misleading in determining the starting dose because of interspecies differences. Add to the conundrum that rapid maturation of multiple systems is ongoing in the neonate. Drugs that are not typically amenable to allometric scaling include “drugs that are highly protein-bound, drugs that undergo extensive metabolism and active transport, drugs that undergo significant biliary excretion (MW > 500, amphiphilic, conjugated), drugs whose targets are subject to inter-species differences in expression, affinity and distribution and drugs that undergo extensive renal secretion.” (Sharma & McNeil, 2010) <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2737649/>

Response to Breakout Question #2

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 - ▶ Can the non-clinical data be extrapolated to inform clinical development, including initial dosing?

Whether the drug is in development or on the market for a different indication will also require a specific formulation to achieve the dose in the neonate. If an oral medication is under consideration, a liquid formulation would be preferred that could be administered by mouth or feeding tube, the latter needed to account for the entry point as different parts of the GI tract effect the absorption of a drug. Parenteral formulations need to take care to have appropriate drug concentrations to limit the volume to be administered by the intravenous, subcutaneous or intramuscular. Typically, verifying the safety of these routes require supportive toxicology studies.

Response to Breakout Question #3

- ▶ For indication X, what information would be needed before starting a clinical trial?
 - ▶ Can existing pediatric or adult studies be extrapolated to neonates?
 - ▶ The FHD adult subjects should have robust PK data that spans a wide range of doses. The minimum anticipated biological effect level (MABEL) may within the doses explored and serves as a potential starting point for extrapolation to the neonatal population. Extrapolations are more relevant if key PD markers behave similarly in the adult and neonatal populations.
 - ▶ If it can be reasonably assumed that disease progression and response to intervention are similar between pediatric and adults populations, and it can be reasonably assumed that the populations have similar exposure – response characteristics, then the effective exposure in adults may be targeted in the pediatric population.

Response to Breakout Question #3

- ▶ For indication X, what information would be needed before starting a clinical trial?
 - ▶ Do the inclusion criteria drive formulation, mode of administration and/or dose?

It depends on large or small molecule as the former are usually parenteral and the latter oral. Formulation importance requires a focus on appropriate volumes to deliver the right dose in a neonate compared to the adult. The conduct of a mass balance study (C^{14} -metabolism) would predict the predominant routes of elimination and would guide use in neonates having either preserved or compromised function of the liver or kidney.

Response to Breakout Question #3

- ▶ For indication X, what information would be needed before starting a clinical trial?
 - ▶ What parameters are needed for constructing a meaningful modelling and simulation tool?
 - ▶ The answer to this question likely depends on what the tool would be used for. The clearance and volume of distribution are key PK parameters from which other parameters can be calculated. If these parameters have been determined at the effective dose in adults then the average concentration over the dosing interval, the area under the concentration – time curve (AUC) during the dosing interval and the half-life are computable parameters which could be useful for targeting effective exposures in a pediatric population.
 - ▶ “*in silico* and other alternative modeling study methods may be developed that can provide preliminary data to inform the design and conduct of PK/PD studies for investigational drugs in pediatric populations. For example, the development of a physiologically-based PK (PBPK) *in silico* model that integrates drug-dependent parameters (e.g., renal clearance, metabolic pathways) and system-dependent parameters (e.g., non-drug parameters such as blood flow rate, protein binding, and enzyme and transporter activities) is one possible approach.” FDA Guidance on Clinical Pharmacology

Response to Breakout Question #4

- ▶ Are there impediments to establishing a master protocol (do multiple approaches exist – comparative effectiveness studies)?
 - ▶ Master Protocol approach considered for adolescents with T2DM – discuss the challenges
 - ▶ Hard to blind given that the different therapies would likely be dosed differently (inhaled, IV, PO) and at different ages, but it would give you a group to compare new therapies in the protocol to.
 - ▶ Extremely difficult to do
 - ▶ Interoperability of the data collection systems would be important to capture the appropriate granularity of data the can help create a robust analysis. Patient-level data is a must as well as the accepted standard of care the neonate is receiving during the study.
 - ▶ IRBs are one impediment as there is a wide range of comfort levels .
 - ▶ Technological capabilities may not be uniform across different NICUs.
- ▶ Is there equipoise?
 - ▶ Should be equipoise since no other therapies work

Response to Breakout Question #5

- ▶ What potential biomarkers and clinical trial endpoints could be used?
 - ▶ Are adequate clinical outcome measures available? If not can they be developed?
 - ▶ Yes
 - ▶ Most studies would need to incorporate death as competing outcome and NDI as either primary or important secondary
 - ▶ noninvasive transthoracic echocardiography is more commonly used in children for its ability to estimate the systolic PAP using the tricuspid regurgitation jet velocity (TRJV) and a modified Bernoulli equation to determine the pressure gradient between the right ventricle (RV) and right atrium.^{75,76} In the absence of tricuspid stenosis or other structural anomalies, the pressure in the RV and pulmonary artery are equal during systole. Qualitative evidence of PH includes flattening of the interventricular septum and hypertrophy/ enlargement of the right heart chambers. However, these are not highly predictive of PAH in the absence of a measurable TRJV and are subject to interobserver variability among echocardiographers.^{77,78} The myocardial performance index (or Tei index), a marker of ventricular dysfunction consisting of the sum of isovolumetric contraction and relaxation times divided by the ejection time, is elevated in primary PH, may be elevated in preterm infants with BPD, and may correlate with BPD severity

Christopher D. Baker, MD,1,2 Steven H. Abman, MD,1,2 and Peter M. Mourani,
MD2,3 DOI: 10.1089/ped.2013.0323

Response to Breakout Question #5

- ▶ What potential biomarkers and clinical trial endpoints could be used?
 - ▶ Are any prognostic, predictive, pharmacodynamic, and safety biomarkers available? Are any regulatory ready?
 - ▶ In preterm infants, postnatal mechanical ventilation and oxygen therapy result in increased expression of antiangiogenic genes such as thrombospondin-1 and endoglin, as well as decreased expression of proangiogenic genes such as VEGF-B, VEGF receptor-2, and the angiopoietin receptor Tie-2.^{35,36}
 - ▶ Additionally, the lungs of human infants with fatal BPD have decreased VEGF levels and markedly dysmorphic vasculature.¹²
 - ▶ Previous studies suggest circulating and vessel wall-derived endothelial progenitor cells (EPCs) contribute to postnatal vasculogenesis.^{38,41} Two distinct EPC subsets—late-outgrowth endothelial colony-forming cells (ECFCs) and angiogenic circulating progenitor cells (CPCs)—are decreased in the umbilical cord blood of preterm infants who go on to develop moderate or severe BPD.^{39,54} Yet, it remains unclear whether cord blood ECFC or CPC levels are biomarkers that can predict BPD severity or PH in the clinical setting.

Response to Breakout Question #5

- ▶ What potential biomarkers and clinical trial endpoints could be used?
 - ▶ Are any prognostic, predictive, pharmacodynamic, and safety biomarkers available? Are any regulatory ready?
 - ▶ ET-ROCK interactions play a key role in impaired endothelial function and angiogenesis in PPHN. Interestingly, findings in this perinatal model of PAH are strikingly different from the results of studies in adult rodent models of PAH, in which increased ROCK activity apparently enhanced vascular growth.⁷⁶ We speculate that, in addition to beneficial effects on smooth muscle cell tone and proliferation, ET-1 receptor blockade may also enhance lung vascular growth in severe PPHN.¹
 - ▶ discriminant metabolites in urine in BPD newborns: lactate, taurine, TMAO, myoinositol (which increased) and gluconate (which decreased).²

¹Gien J, Tseng N, Seedorf G, Roe G, Abman SH. Gien J, Tseng N, Seedorf G, Roe G, Abman SH. *Pediatr Res* 2013;73(3):252–262; 2 V. Fanos et al. *J Matern Fetal Neonatal Med*, 2014; 27(S2): 39–45

DETAILED RESPONSES

DETAILED RESPONSES

Response to Breakout Question #2

- ▶ For indication BPD, what non-clinical studies need to be carried out prior to designing clinical trials of new and/or existing drugs?
- ▶ **Basic Science: Mechanistic and pathogenic cause**
 - ▶ What juvenile animal toxicity studies are needed?
 - ❑ core safety pharmacology studies (cardiovascular, CNS, respiratory)
 - ❑ repeat-dose toxicity studies,
 - ❑ genotoxicity battery,
 - ❑ fertility studies
 - ❑ pre- and postnatal development studies.

Juvenile toxicity studies are conducted on a case-by-case basis

- ❑ Small molecules: the rat is generally the species employed.
- ❑ Large molecules for which monkey may be the only appropriate species due to immunogenicity issues with rodents pose additional challenges.