



## September 2008: VOLUME 6, NUMBER 1

### Synthetic Surfactants

#### In this Issue...

Neonatal surfactant therapy has not only dramatically reduced mortality and morbidity from respiratory distress syndrome (RDS) among preterm infants, but has also been shown to be effective in improving pulmonary function in newborns with acute respiratory distress syndrome (ARDS) secondary to meconium aspiration, neonatal pneumonia, persistent pulmonary hypertension (PPH) of the newborn, and pulmonary hemorrhage. In neonatal RDS surfactant deficiency predominates, whereas in ARDS surfactant inactivation by proteins and phospholipases causes secondary surfactant dysfunction. Although dipalmitoyl phosphatidylcholine (DPPC) and phosphatidylglycerol (PG) constitute the main phospholipid components in surfactant, its biophysical activity depends to a large extent on the presence of the hydrophobic surfactant protein B (SP-B) and to a lesser extent on the extremely hydrophobic surfactant protein C (SP-C). The water-soluble surfactant proteins A (SP-A) and D (SP-D) are important for host defense, but the presence of SP-B is critical for reducing surface tension within the alveolus and maintaining lung volume at end-expiration. In fact, hereditary SP-B deficiency is lethal in humans, whereas mutations in the gene encoding SP-C may cause interstitial lung disease and increase susceptibility to infection.

Current clinical surfactants are produced by extracting lung lavages or lung tissue from cows or pigs and contain most of the surfactant lipids, except cholesterol, and variable amounts of SP-B and C.<sup>1</sup> In this issue we discuss the progress achieved in the development of new synthetic surfactants.<sup>2-5</sup> Potential advantages of synthetic surfactants are: (1) less batch-to-batch variability in composition and fewer quality control issues; (2) lower production costs; (3) no concerns about transmission of animal infectious agents and immunological reactions; and (4) the potential to improve surface activity by selected changes in the composition.



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### **Guest Faculty Disclosure**

**Dr. Walther** has no relevant financial relationships to disclose.

**Dr. Waring** has no relevant financial relationships to disclose.

### **Unlabeled/Unapproved Uses**

Dr. Walther has indicated that he does not reference any off-label or unapproved uses of drugs or products in this publication.

Dr. Waring has indicated that he does reference the off-label or unapproved use of synthetic surfactant in this publication.

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## LEARNING OBJECTIVES

**At the conclusion of this activity, participants should be able to:**

- Describe to colleagues the potential advantages of synthetic over natural lung surfactant
- Discuss with colleagues how SP-B and SP-C analogues may enhance the surface activity of synthetic surfactants
- Summarize for colleagues the potential of phospholipase-resistant phospholipids in synthetic surfactants to reverse surfactant inactivation

## COMMENTARY

Synthesis of small surfactant protein analogues has provided new insights in protein structure and function and its interaction with lipids.<sup>3-5</sup> Walther et al. (reviewed in this issue) report how lipid mixtures affect the efficacy of surfactant protein analogues.<sup>6,7</sup> Although simple lipid mixtures like dipalmitoyl phosphatidylcholine (DPPC): palmitoyl oleoyl PG (POPG) 70:30 (w/w) and DPPC:POPG:palmitic acid (PA) 69:22:9 (w/w/w) show excellent in vitro and in vivo surface activity with native surfactant proteins or selected synthetic peptides, use of a native lipid mixture with more unsaturated and less charged phospholipids, with cholesterol and only minor amounts of palmitic acid, further improved the efficacy of surfactant proteins and peptides.<sup>6</sup> Synthetic lipid mixtures based on the composition of native surfactant may therefore be more appropriate in the formulation of synthetic surfactant peptides.

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Chang et al. (reviewed in this issue) report on a new class of phospholipase-resistant DPPC and PG (phosphono)lipids, such as the DPPC mimic DEPN-8, which offer the opportunity to design synthetic surfactants for use in ARDS where surfactant dysfunction prevails.<sup>8-10</sup>

Human SP-B contains 79 amino acids,  $\alpha$ -helical structures in the amino- (N-) and carboxy- (C-) terminal domains, multiple polar residues interacting with phospholipids, and forms dimers and oligomers through intermolecular cysteine-linked sulfhydryl bridges.<sup>3,4</sup> KL<sub>4</sub> is a 21-amino acid peptide with an  $\alpha$ -helical structure built with the hydrophobic amino acid leucine and the cationic amino acid lysine meant to mimic the functional structure of SP-B.<sup>11</sup> The available data suggest that the KL<sub>4</sub>-based replacement surfactant lucinactant (Surfaxin<sup>®</sup>) is an effective synthetic surfactant, which, in contrast with natural surfactant, needs extensive preparation before it can be drawn up into a syringe for administration (Sinha et al., reviewed herein).<sup>12</sup> The molecular mechanism by which KL<sub>4</sub> interacts with lipids remains unclear.<sup>13</sup> Waring et al. (reviewed herein) report how a novel, more advanced synthetic SP-B analogue called “Mini-B” (a disulfide-linked 34-amino acid construct based on the primary sequences of the N- and C-terminal domains of SP-B) exceeds the in vitro and in vivo activity of native SP-B.<sup>14</sup>

Human SP-C is smaller than SP-B (35 amino acids), and has two palmitoyl moieties and one  $\alpha$ -helical structure. SP-C analogues have been produced by cloning (eg, recombinant human SP-C [rhSP-C] used in Venticute<sup>®</sup> surfactant) or peptide synthesis (eg, SP-C<sub>ff</sub>, SP-C<sub>33</sub>).<sup>3-5,15,16</sup> Production of SP-C analogues is complicated by the presence of the palmitoyl residues at the N-terminal domain and aggregation by transformation from a dominant  $\alpha$ -helical conformation into  $\beta$ -amyloid structures that are not surface active. In rhSP-C and SP-C<sub>ff</sub>, two cysteines with palmitoyl residues have been replaced by phenylalanine. To minimize the loss of  $\alpha$ -helix, Almlen et al. (reviewed herein) designed a shortened synthetic form of SP-C (SP-C<sub>33</sub>) with a number of different modifications. In SP-C<sub>33</sub> the palmitoyl cysteine residues were replaced with serines, a leucine at position 14 with lysine, and a stretch of valine residues (positions 15–21 and 23–28) with an extended polyleucine sequence.<sup>17,18</sup> Although SP-C<sub>33</sub> mimics human SP-C function in vitro and in vivo experiments, SP-B is necessary to obtain alveolar stability at end-expiration in ventilated preterm rabbits.<sup>18</sup>

Wang et al. and Walther et al. (both reviewed herein) recently investigated combinations of native surfactant proteins, peptide analogues, and the phospholipase-resistant DPPC mimic DEPN-8.<sup>10,19,20</sup> This work demonstrates the potential of these combinations to combat both surfactant deficiency and dysfunction.

Building upon the relatively limited functionality of first generation synthetic surfactants such as the KL<sub>4</sub>-surfactant lucinactant and the rhSP-C surfactant, recently developed novel SP-B and C peptides (such as Mini-B and SP-C<sub>33</sub>), formulated in novel phospholipase-resistant lipid mixtures, promise better surface activity under conditions of surfactant deficiency and dysfunction and offer more advanced surfactant treatment for a wider range of lung diseases.

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## LIPIDS COMPOSITION AFFECTS SURFACE ACTIVITY OF SYNTHETIC SURFACTANTS

Walther FJ, Hernández-Juviel JM, Gordon LM, Waring AJ, Stenger P, Zasadzinski JA. **Comparison of three lipid formulations for synthetic surfactant with a surfactant protein B analog**. *Exp Lung Res*. 2005;31(6):563-579.

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The investigators tested the optimum lipid composition for 2% dimeric SP-B1-25, a peptide based on the N-terminal domain of human SP-B, by comparing the effects of natural lung lavage lipids extracted from the clinical surfactant calfactant (Infasur® Lipids, InL), a synthetic equivalent of IL (sIL), and a standard lipid mixture consisting of DPPC:POPG:PA 69:22:9 % (Tanaka Lipids, TL). The ability of the mixtures to lower surface tension effectively was measured in vitro using a captive bubble surfactometer, and in vivo effectiveness was assessed in an animal model using ventilated surfactant-deficient rats.



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Minimum surface tension measured with the captive bubble surfactometer was similar for the three SP-B<sub>1-25</sub> surfactant preparations and calfactant. Oxygenation and lung volumes were consistently higher in rats treated with calfactant and SP-B<sub>1-25</sub> in InL or sIL than in rats treated with SP-B<sub>1-25</sub> in TL. Spectroscopy showed abnormal secondary conformations for SP-B<sub>1-25</sub> in TL and viscosity measurements a higher viscosity as possible causes for the reduced lung function.

This study demonstrated that lipid composition markedly affects surface activity of synthetic surfactants and emphasizes the important role of lipids in the efficacy of a surfactant peptide.

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## NOVEL PHOSPHONOLIPIDS RESISTANT AGAINST PHOSPHOLIPASES

Chang Y, Wang Z, Schwan AL, Wang Z, Holm BA, Baatz JE, et al. **Surface properties of sulfur- and ether-linked phosphonolipids with and without purified hydrophobic lung surfactant proteins.** *Chem Phys Lipids*. 2005;137(1-2):77-93.

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The authors studied the surface activity of 2 novel C16:0 sulfur-linked phosphonolipids (S-lipid and SO<sub>2</sub>-lipid) and 2 ether-linked phosphonolipids (C16:0 DEPN-8 and C16:1 UnDEPN-8) in combination with bovine SP-B and SP-C. These synthetic phosphonolipids all demonstrated better adsorption and respreading than DPPC on a Wilhelmy balance. Surfactants containing DEPN-8 or SO<sub>2</sub>-lipid plus 0.75% of SP-B and 0.75% of SP-C had dynamic surface activity on the pulsating bubble surfactometer equal to that of calfactant. Surfactants containing DEPN-8 or SO<sub>2</sub>-lipid plus 1.5% SP-B also had a very high surface activity, but less so than in the presence of both SP-B and SP-C. Surfactants containing DEPN-8 or SO<sub>2</sub>-lipid plus 0.75% SP-B and 0.75% SP-C were chemically and biophysically resistant to phospholipase A<sub>2</sub> (PLA<sub>2</sub>), whereas calfactant was severely inhibited by PLA<sub>2</sub>.

These findings are important because phospholipases not only degrade phospholipids in surfactant, but also generate chemical byproducts like free fatty acids and lyso-phosphatidylcholines (lyso-PCs) that severely inhibit surfactant activity. The high surface activity and inhibition resistance of synthetic surfactants containing DEPN-8 or SO<sub>2</sub>-lipid plus SP-B and SP-C are promising for the development of new synthetic surfactants for ARDS, where lytic phospholipases are induced.

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## KL<sub>4</sub>: SURFACTANT PEPTIDE RESEMBLING ONE OF THE AMPHIPATHIC DOMAINS OF SP-B

Sinha SK, Lacaze-Masmonteil T, Valls i Soler A, Wiswell TE, Gadzinowski J, Hajdu J, et al; Surfaxin Therapy Against Respiratory Distress Syndrome Collaborative Group. **A multicenter, randomized, controlled trial of lucinactant versus poractant alfa among very premature infants at high risk for respiratory distress syndrome.** *Pediatrics*. 2005;115(4):1030-1038.

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Lucinactant (Surfaxin®) is a synthetic peptide-containing surfactant that contains a 21-amino acid peptide (leucine and lysine repeating units, KL<sub>4</sub> peptide) designed to mimic human SP-B. This hydrophobic peptide was designed to approximate the balance of hydrophobic and hydrophilic residues found in native SP-B. In a randomized clinical trial (the STAR study), 119 infants born between 24 and 28 weeks of completed gestation and with birth weights between 600 and 1250 grams, received lucinactant and 124 infants received poractant alfa (Curosurf®) within 30 minutes of life. All infants were electively intubated at birth for this study. Outcome at 36 weeks postmenstrual age was similar in both groups, 19 (16.0%) infants in the lucinactant group died and 77 (64.7%) were alive without bronchopulmonary dysplasia (BPD) versus 23 (18.5%) deaths and 83 (66.9%) survivors without BPD in the poractant alfa group. Dosing complications and the incidences of common complications of prematurity, such as intraventricular hemorrhage (grades 3 and 4) and cystic periventricular leukomalacia, were also comparable in both groups. This study suggests that lucinactant is as safe and efficient for the treatment of RDS in very preterm infants as poractant alfa. An interesting point in this study is that poractant alfa can be quickly drawn up in a syringe for administration, whereas lucinactant is stored at 4°C as a gel and needs to be heated at 44°C in a warming cradle for 15 minutes and then shaken to be converted into liquid form.

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## MINI-B: $\alpha$ -HELICAL AMINO- AND CARBOXYC-TERMINAL DOMAINS ARE KEY TO SP-B FUNCTION

Waring AJ, Walther FJ, Gordon LM, Hernandez-Juviel JM, Hong T, Sherman MA, et al. **The role of charged amphipathic helices in the structure and function of surfactant protein B.** *J Pept Res*. 2005; 66:364-374.

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The amino- (N-) and carboxy- (C-) terminal domains of SP-B participate in critical surfactant activities. Surfactant preparations containing either synthetic peptides representing these SP-B domains or full-length SP-B improve oxygenation and/or lung compliance in surfactant-deficient animals. The authors designed, produced and tested Mini-B, a synthetic construct (34-residues) based on the primary sequences of the N- and C-terminal domains and the disulfide cross-linkages of native SP-B. Both isotope-enhanced Fourier transform infrared spectroscopy and molecular modeling confirmed that Mini-B contained charged amphipathic  $\alpha$ -helices similar to those in native SP-B. Mini-B in surfactant lipid mixtures exhibited excellent in vitro surface activity, with spread films showing near-zero minimum surface tensions during cycling using captive bubble surfactometry. In experiments with surfactant-deficient rats, Mini-B improved oxygenation and lung compliance and compared favorably with that of full-length SP-B. Mini-B variants (ie, reduced disulfides or cationic residues replaced by uncharged residues) or Mini-B fragments (ie, unlinked N- and C-terminal domains) produced greatly attenuated in vivo and in vitro surfactant properties, demonstrating that the 3D structure and charge distribution of the amphipathic  $\alpha$ -helical N- and C-terminal domains are key to SP-B function. Mini-B peptide has great potential as a SP-B mimic in synthetic surfactants.

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## BOTH SP-B AND SP-C ARE NECESSARY TO ESTABLISH ALVEOLAR STABILITY IN PREMATURE RABBITS WITH RDS

Almlén A, Stichtenoth G, Linderholm B, Haegerstrand-Björkman M, Robertson B, Johansson J, et al. **Surfactant proteins B and C are both necessary for alveolar stability at end expiration in premature rabbits with respiratory distress syndrome.** *J Appl Physiol.* 2008;104(4):1101-1108.

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The individual and combined effects of SP-B and SP-C were evaluated in ventilated premature rabbits. Synthetic surfactants composed of synthetic phospholipids mixed with equivalent amounts of either porcine SP-B or SP-C, or SP-C<sub>33</sub>, did not stabilize the alveoli at the end of expiration. Treatment with surfactants containing both SP-B and SP-C, or SP-B and SP-C<sub>33</sub>, approximately doubled lung gas volumes. The tidal volumes were similar in all groups receiving surfactant.

These data suggest that SP-B and SP-C exert different physiological effects, and that both proteins are needed to establish alveolar stability at end-expiration. An optimal synthetic surfactant therefore requires the presence of mimics of both SP-B and SP-C. Furthermore, this study shows that the SP-C mimic SP-C<sub>33</sub> is as efficient as native SP-C in improving surface properties of lipids mixtures and in increasing lung compliance in surfactant-deficient rabbits.

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## NATIVE SP-B/C OR MINI-B ARE HIGHLY ACTIVE IN PHOSPHOLIPASE-RESISTANT LIPIDS

Wang Z, Chang Y, Schwan AL, Notter RH. **Activity and inhibition resistance of a phospholipase-resistant synthetic surfactant in rat lungs.** *Am J Respir Cell Mol Biol.* 2007;37(4):387-394.

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Wang et al. investigated the activity and inhibition resistance in excised rat lungs of a synthetic surfactant preparation containing the phospholipase-resistant DPPC mimic DEPN-8 plus 1.5% bovine SP-B/C compared to calfactant. DEPN-8 + SP-B/C surpassed calfactant in normalizing lung compliance in lavaged excised lungs in the presence of phospholipase A<sub>2</sub>, and was equally effective in the absence of inhibitors or in the presence of the surfactant inhibitor serum albumin. These findings were consistent with surface activity measurements on the pulsating bubble surfactometer.

Walther et al. compared surface activity and resistance to phospholipase degradation of a synthetic surfactant containing DEPN-8 + 1.5% Mini-B with CLSE. In contrast with CLSE, DEPN-8 + Mini-B was fully resistant to degradation by phospholipase A<sub>2</sub> in vitro. Mini-B



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had significant binding affinity for DEPN-8. DEPN-8 + Mini-B and CLSE both reached low minimum surface tensions at surfactometry and this did not change in the presence of equivalent amounts of serum albumin.

These results show that DEPN-8 and Mini-B form an interactive binary molecular mixture with very high surface activity and the ability to resist degradation by phospholipases in inflammatory lung injury. These characteristics are promising for the development of synthetic surfactants for treating RDS and ARDS.

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## Learning Objectives — [back to top](#)

At the conclusion of this activity, participants should be able to:

- Describe to colleagues the potential advantages of synthetic over natural lung surfactant
- Discuss with colleagues how SP-B and SP-C analogues may enhance the surface activity of synthetic surfactants
- Summarize for colleagues the potential of phospholipase-resistant phospholipids in synthetic surfactants to reverse surfactant inactivation

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