**Therapeutic lung surfactants as carriers for other
therapeutics– a matter of vision, courage and determination**

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**Therapeutic lung surfactants as carriers for other therapeutics– a matter of vision, courage
and determination**

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The need for a surface tension reducing agent in the lung was first recognised by von Neergard in 1929 [1]. He made this deduction after applying the law of Young-Laplace (which, as early as 1805, described the effects of surface tension forces at curved interfaces) to the proper function of alveoli and bronchioli. Our appreciation and understanding of this SURFace ACTive AgeNT (Surfactant) over the subsequent eighty years, has led to the successful development of treatments for respiratory distress syndrome in preterm infants. The implementation of which was responsible for the single greatest reduction in infant mortality last Century. However, increased surface tension due to immaturity is not the only problem of preterm lungs, which combined with infection, inflammation, oxidative stress and failure of normal alveolarisation seriously impede normal lung development. To address these additional complications, a range of treatments from steroids and antibiotics, to growth factors for either systemic or topical administration (via inhalation) are either in use, or under investigation [2, 3]. The question is, are we courageous, insightful and determined enough to exploit the unique biophysical and biochemical properties of surfactant for use as a carrier of topical lung treatments as well?

In their study presented in this issue, Dani and co-workers address this possibility using a natural porcine surfactant derivative (Curosurf®) as the carrier for beclomethasone, an anti-inflammatory drug, in an animal model of preterm delivery [4]. They demonstrate not only that co-treatment is feasible, but that it is also therapeutically superior to surfactant administered alone. Maintained oxygenation parameters together with improved mean airway pressure, blood pH and pCO₂ as well as decreased inflammatory cells and oxidation products, suggest that beclomethasone was both pharmacologically active, and efficiently delivered to the periphery of the lung. While Dani et al used mechanical ventilation to demonstrate the efficacy of their approach, it is worth mentioning that techniques for surfactant administration without mechanical ventilation are so well developed that clinical use of surfactant as a carrier is now a realistic goal [5, 6].

Currently, the only alternative to systemic treatment of the lungs is via inhalation, which, in the case of glucocorticoids, bronchodilators and antibiotics, is well established. Patients range from

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preterm infants to adults, and applications include the treatment or prevention of bronchopulmonary dysplasia, obstructive lung diseases and microbial colonisation. As early as 1991 Karasch et al used surfactant as a vehicle for particle deposition to the lung periphery [7], and in 2001 Haitzma et al commented that “Although use of surfactant as a carrier is relatively new and the amount of data is limited, a few advantages are already becoming clear” [8]. In the year 2009, we are still snared by the old paradigms separating surfactant solely as a treatment for reducing surface tension from other topical treatments. However, combining the excellent spreading properties of natural surfactants, with their increasingly documented immunomodulatory properties [9] - or that of their optimized synthetic analogues – for the delivery of other therapeutics to the lungs, presents an exciting tool with huge potential.

In contrast to other liposomes that do not fulfil the requirements for alveolar treatment, mammalian surfactant is a complex mixture comprising 80% phospholipid, together with neutral lipids and four specific proteins (SP). Of the phospholipid component, 80-85% are phosphatidylcholine (PC) molecular species. Three of these PC species, namely dipalmitoyl-PC (PC16:0/16:0), palmitoyl-myristoyl-PC (PC16:0/14:0) and palmitoyl-palmitoleoyl-PC (PC16:0/16:1), are specifically enriched in lung surfactant [10]. PC16:0/14:0, PC16:0/16:1 together with less abundant plasmalogen components, as well as high SP-B and -C concentrations, improve surface tension function and decrease surfactant viscosity under dynamic conditions [11, 12].

Improving the biophysical properties of artificial surfactant by modifying its lipidomic profile to resemble natural surfactant is well described [12, 13]. Consistent with this Dani et al used a natural surfactant in their study present here [4]. Additionally, new evidence describing changes in surfactant PC composition during development [14] as well as detailed studies demonstrating the diverse but nevertheless highly regulated PC compositions present in air-breathing animals [15], challenge age old paradigms which have hitherto dictated therapeutic surfactant compositions. Taken together, these findings prompt serious investigation into ‘optimal’ surfactant composition. In particular, the impact of the previously described lesser abundant components and their influence on adsorption,

surface pressure, and viscosity, as well as their effects on efficient spreading and distribution to the lung's periphery, must be taken into consideration [8, 10, 12]. Features of the appended drugs, for example lipophilic glucocorticoids vs. hydrophilic antibiotics [8], will also have to be taken into account when using or developing surfactants as carriers. Although Dani et al [4] demonstrate the successful combination of two well established therapeutics, a natural porcine surfactant and a glucocorticoid (beclomethasone), they highlight the potential risks associated with generic glucocorticoid treatment, despite specific delivery of the drug [4]. However, recent work identifying the factors responsible for inducing epithelial cell differentiation upon glucocorticoid stimulation, preventing epithelial injury and inversely correlating with bronchopulmonary dysplasia (such as keratinocyte growth factor), present hope for exciting future therapeutic target drugs for delivery by surfactant [2, 3]. In summary, the study presented by Dani et al in this issue, provides further evidence to support clinical trials in infants with IRDS, which may lead to the implementation of such treatment modalities in our neonatal intensive care units. We would encourage serious efforts to replace current systemic and inhalation treatment (wherever applicable) with surfactants as carriers, and express our hope that this approach will not vanish into the misty mountains of endless animal studies.

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