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The International Week of Surfactant Research: Increasing knowledge about surfactant and unexploited opportunities

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Surfactant is not a new discovery in biology and medicine. In 1929, Neergard et al. suggested that physical properties of alveolar surface are an important factor that influences lung functions [1]. It quickly became clear that surfactant was constituted of a complex proteo-lipid mixture necessary to lower alveolar surface tension [Fig. 1]. Thus, surfactant replacement therapy for respiratory distress syndrome (RDS) due to its primary deficiency in preterm neonates was pre-clinically and clinically tested for the first time in 1972 and 1980, respectively [2,3]. At that time, RDS and acute respiratory distress syndrome (ARDS) were considered as the typical features of two different types of respiratory failures in neonates and adults, respectively.

Then, the enthusiasm and expertise accumulated in preterm neonates with RDS prompted to study surfactant in children with completely different disorders, such as pediatric (PARDS) and neonatal ARDS (NARDS). Of note, these syndromes were not even recognized due to the lack of precise clinical definitions when surfactant was clinically studied (the PALICC and Montreux definitions [4,5] were not yet available at that time). Thus, these studies were performed following an understandable enthusiasm due to the success of surfactant replacement for RDS, but without adequate pre-clinical and clinical background. Furthermore, during 90s and early 2000, surfactant has also been clinically investigated in adult patients suffering from ARDS [6].

However, the natural history of surfactant seems to have had a U-shape. In fact, an initial great interest has accelerated its clinical development in neonatal medicine which becomes quickly successful. Then, the lack of a spectacular effect of surfactant for ARDS in patients of various age (as compared to what has been shown for RDS in preterm neonates) has slowed down the process and attenuated the enthusiasm of surfactant use in adults. However, the quick and stunning success of surfactant as RDS treatment is one of its kind and there are not many similar examples of drug discovery in medicine: if this has been extremely positive, it has also represented a challenging comparator and led to several

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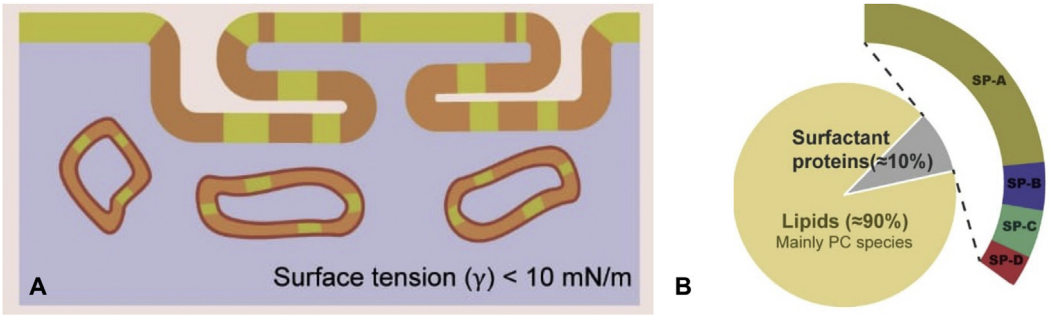

Fig. 1 **Main characteristics of surfactant.** Surfactant is a mixture composed of proteins (10 %) and lipids (90 %, mainly phosphatidylcholine species) forming a complex structure made of membranes capable to reduce alveolar surface tension (to at least <10 mN/m) and open the alveoli to make gas exchange possible. Several other several biological (anti-inflammatory, immunomodulating and anti-infective) functions are also played and are interconnected. Artwork kindly prepared by Alejandro Alonso (PhD) and provided by Chiara Autilio (PhD).

mistakes. For instance, a quick clinical application has been sought, bypassing adequate translational and basic pharmacological research: animal models to study different subtypes of ARDS have not been well characterized until recent years and dose finding studies are still lacking [7–9].

A first mistake was due to the dissociation between preclinical and clinical research. In fact, while some groups were performing important studies to understand surfactant biology, their findings have not been considered in the drug development process. For instance, over the years many new concepts on surfactant biology have been clarified, such as its catabolism and the role of phospholipases [10], the importance of hydrophobic and hydrophilic surfactant proteins [11–13], the complex surfactant phospholipid profile and the role of temperature [14–16], or the interaction between surfactant and other drugs [17–21] that might increase its function. Surfactant components are capable to modulate immune response and this may have wide and relevant consequences [22]. Other issues are better clarified, such as the importance of drug volume and ventilatory pressure on surfactant distribution and the difficulties regarding its nebulization [23]. Following this, it became evident how surfactant can be useful as drug carrier in many lung disorders [24], but this property is still clinically unexploited with the only exception of surfactant-vehicled budesonide, which seems useful to prevent bronchopulmonary dysplasia but only in neonates subjected to long and aggressive ventilation with relevant lung tissue inflammation [25]. As physiopathology and biology of lung disorders may vary, the use of surfactant as drug carrier still requires a huge investment in terms of joint translational and clinical research with explanatory projects dedicated to each different target condition. Failing to have translational and clinical research advancing together, unavoidably prevents the achievement of drug development.

The other example is the general carelessness about surfactant dose [9] and the lack of study to define the optimal dose for ARDS patients, as it should be for any investigational drug to treat any condition.

More and above this, a lack of cross-disciplinary awareness and interactions has been unfortunately evident overtime. In fact, researchers in surfactant biology have not been aware of ongoing clinical studies in adults and could have not contributed to their design. Clinical researchers have not benefited from mutual exchanges with basic science investigators, and, consequently, the clinical unmet need have never been matched with the increasing knowledge on surfactant biology.

Last but not least, many in the neonatal medicine world may have thought that surfactant was there to stay since it is quite well functioning, but did not explore, in a rigorous way, how to optimize surfactant replacement for RDS or if surfactant could be used to treat other respiratory disorders. Obviously, the biggest lack of crosstalk has been developed between the world of neonatal and adult intensive care, since they were not aware of each other's knowledge and clinical problems. If these two worlds would have interacted more, some respective errors could have been avoided and a deeper crosstalk with the world of translational research would have likely promoted some successful results, as it happens in other fields of medicine.

Despite all this, the application of surfactant therapy in contexts other than RDS is promising and there is the impression that a bulk of knowledge and a promising therapy is being forgotten. In fact, the European Society for Pediatric and Neonatal Intensive Care recognized that surfactant therapy has shown encouraging signal in patients with PARDS and NARDS [23]. Similar findings have been observed in adults with primary ARDS [26].

The International Week on Surfactant Research (IWSR, see: https://www.mcascientificevents.eu/surfactantresearch/) has been launched in 2020 expressly with the aim to reduce this lack of cross-disciplinary of awareness and interactions. IWSR has been and will always be a meeting place for biologists, pharmacologists, neonatal, pediatric and adult intensivists coming from different settings. In fact, IWSR aims to convene people from the clinical field, the academy and the industry. We believe that this is the best way to let the knowledge

advancing and providing new solutions to clinical unmet needs. Similar attempts have been tried and recognized to be useful by regulatory agencies [27]. Surfactant is a potentially very useful drug with an extremely complex biology and pharmacology, but is also an essential medicine as recognized by the World Health Organization. The second edition of IWSR is in preparation and will be held by the end of 2021. IWSR has been a great success and has seen the participation of hundreds of clinicians and researchers from different fields. The pandemics has not reduced the interest in this field and even increased as surfactant is being currently investigated for ARDS due to COVID-19 [28]. The virtual nature of the event has facilitated the participation and exchanges by reducing expenses and allowing contributions from very far countries all over the world.

We all share the obligation to make surfactant as much available and efficacious as possible: in this number of the *Biomedical Journal* we present some of the main subjects of the 1st edition of IWSR. These include relevant cutting-edge topics and have been addressed by key opinion leaders from the different areas described above.

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