Standing on shoulders

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It is at the crossroads of different scientific fields that the most interesting studies are created
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If I have seen further it is by standing on the shoulders of giants.

– Isaac Newton

This saying was already a popular metaphor in the middle ages, and still is. A contemporary meaning of this would be: one who discovers by building on discoveries made by predecessors. And in this issue of the *European Respiratory Journal*, CHANG *et al.* [1] have done exactly that. Appreciating and using the ideas of a classical physiological study [2], and combining this with the results of modern molecular biology they demonstrate how, at the crossroads of two completely different scientific fields, an added value is created that brings us forward in understanding one of the most fascinating phenomena in respiratory medicine: lung growth and repair.

Obviously, ''classical'' and anatomical studies have been regularly used to confirm anatomical and pathological concepts, using lung function data to assess growth of lungs and airways in healthy children [3, 4], children with asthma [5] or preterm infants [6]. However, the study by CHANG *et al.* [1] is far more advanced because it introduces new applications of novel infant lung function techniques and incorporates these with classic physiological concepts [2], while combining them with advanced subtyping of progenitor cells.

In children aged 3–28 months, membrane diffusion capacity and capillary blood volume increased with body size, but the membrane resistance to diffusion relative to the total pulmonary resistance to diffusion remained similar with growth. In addition, the authors observed that the ratio of pro-angiogenic to nonangiogenic circulating haematopoietic stem/progenitor cells (CHSPCs) was related to a higher pulmonary diffusion capacity, as well as a higher pulmonary capillary vascular volume [1].

Because alveolar development is highly dependent on the formation of the pulmonary microvasculature, it is crucial for the understanding of lung growth to assess which factors, hormones and cells co-determine pulmonary angiogenesis and vasculogenesis. Probably even more important is that this knowledge may be the key to novel treatments that enhance alveolar formation. These progenitor cells seem to play a most important role here, and this may apply to premature infants [7], children with severe lung disease [8] and, perhaps, also adults [9]. Other findings, such as observations that CHSPCs are increased in menstruating females who exhibit a cyclic increase of diffusing capacity [10], and that infusion of angiogenic cells helps to restore alveolar development in a mouse model of bronchopulmonary dysplasia [11], also strongly suggest that angiogenic cells play a role in developing or restoring the pulmonary vasculature and may enhance alveolar formation indirectly.

In addition, these observations are in line with older studies. A large interindividual variability in the number of alveoli was recognised decades ago [12–14] and one can speculate that this is partly due to biological variation in the numbers and/or ratio of pro- and non-angiogenic CHSPCs. Also the greater

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capillary volume found in males compared to females in infancy [1], fits very well with the larger numbers of alveoli found in males compared to females [13, 14].

The research into the possible medical use of stem cells has exploded and was the reason to honour top researchers with the Nobel prize [15]. Although it will take many years before novel treatment modalities are proven safe and effective, progress is being made and, even for a complex organ such as the lung, the prospects look good. It seems plausible then that the ''classical old fashion physiology'' will remain necessary to assess the functional benefits of such highly advanced treatment modalities of the 21st century.

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