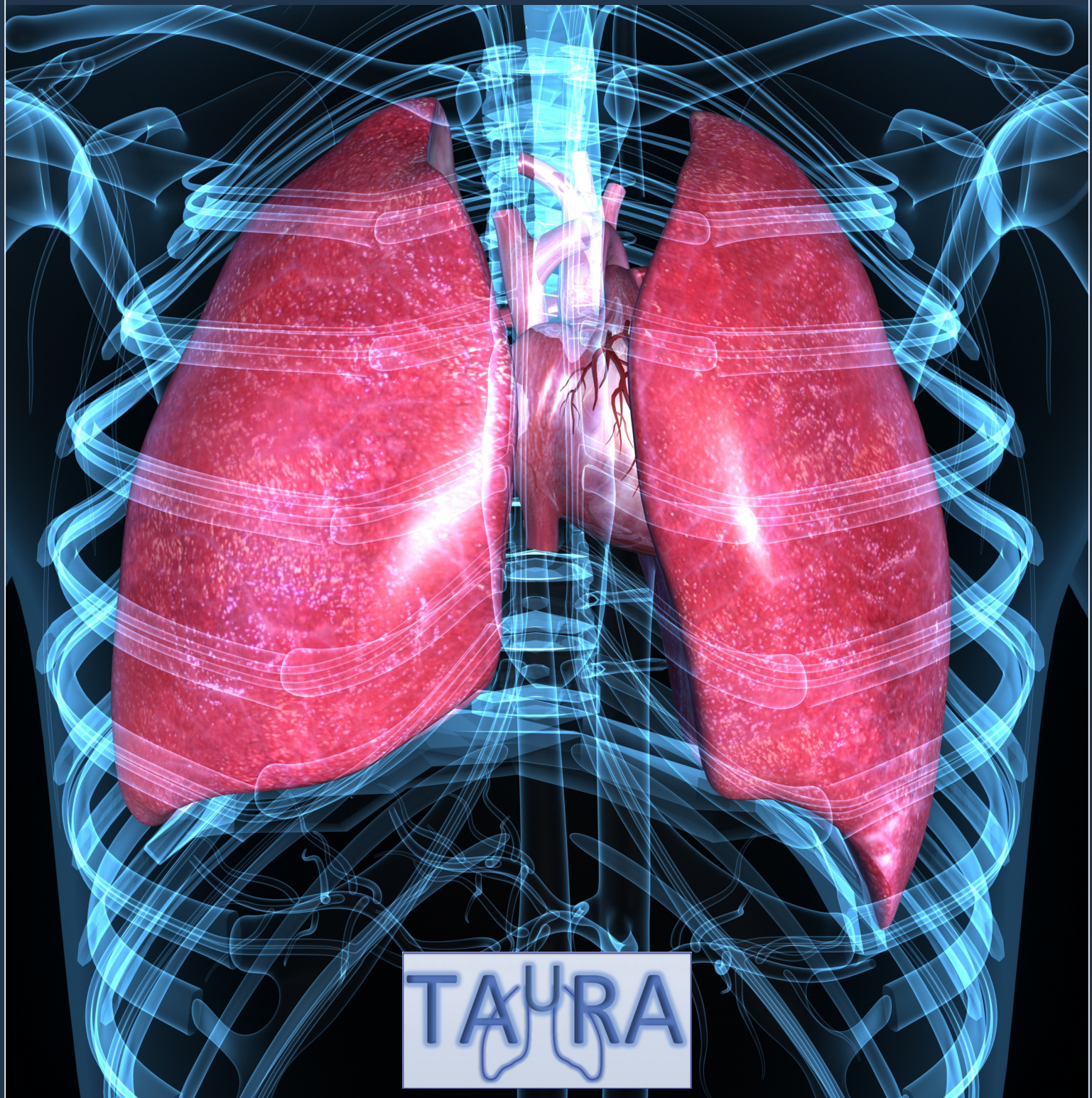# ACUTE RESPIRATORY DISTRESS SYNDROME

CHALLENGES FOR TRANSLATIONAL RESEARCH AND
OPPORTUNITIES FOR PRECISION MEDICINE

TAURA

Acute respiratory distress syndrome:
challenges for translational research and opportunities for precision medicine

ARDS: a complex, under-recognized, and life-threatening syndrome

Acute respiratory distress syndrome (ARDS) was first described as a clinical syndrome by David Ashbaugh, Thomas Petty, and coauthors in 1967. The next 20 years of ARDS research focused primarily on pathophysiology and pathogenesis, including both animal and human studies. Several refinements of the definition of ARDS were published including the 4-point acute lung injury score in 1988, the American European Consensus definition in 1994, and the latest Berlin definition of ARDS in 2012.

ARDS is defined using the clinical criteria of bilateral pulmonary opacities on chest radiograph, arterial hypoxemia [partial pressure of arterial oxygen (PaO_2) to fraction of inspired oxygen (FiO_2) ratio $\leq$ 300 with positive end-expiratory pressure (PEEP) $\geq$ 5 cmH_2O] within one week of a clinical insult or new or worsening respiratory symptoms, and the exclusion of cardiac failure as the primary cause. ARDS is a syndrome of pulmonary edema and inflammation that often includes non-pulmonary organ dysfunction. Although ARDS is present in more than 10% of intensive care unit (ICU) admissions and in nearly 25% of ICU patients requiring mechanical ventilation, it is still an under-recognized challenge for clinicians, with a hospital mortality rate of 35-45%. Beyond such a high mortality rate, ARDS is associated with greater healthcare utilization, reduced quality of life among survivors and worse long-term physical and cognitive outcomes.

A need for translational research to discover disease modifying therapies for ARDS

Fifty years after its first clinical description, and despite intense research, the identification of an effective ARDS therapy has failed to date. Major progress has been made in reducing mortality from ARDS with "lung-protective" ventilation, using a tidal volume of 6 mL per kg of predicted body weight and a plateau airway pressure of less than 30 cm H_2O. In more severely hypoxemic patients with ARDS, neuromuscular blockade and prone positioning have further reduced mortality, probably by extending the therapeutic effects of lung protective ventilation. Fluid-conservative therapy has also increased ventilator-free days in patients with ARDS. The lack of success of pharmacological therapies for ARDS, however, presents a continued challenge in the field and many negative trials on pharmacological agents, including beta-agonists, corticosteroids, anticoagulants, and surfactant replacement, among others, have now been performed.

In 2003, it was already suggested by a National Heart, Lung, and Blood Institute working group on future directions for research into acute lung injury that an improved understanding of disease heterogeneity, through use of biological approaches to translational models, would provide major new insight into the pathogenesis and resolution of ARDS. Translation of basic research findings to clinical practice remains daunting because of the heterogeneity and complexity of ARDS. Recent basic studies have done well to mirror the multiple-hit hypothesis for ARDS

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pathogenesis, which states that lung injury occurs most readily with concomitant physiological insults that prime the immune system for an amplified response to mechanical lung stress. However, young, typically healthy animals are managed right after ARDS onset for limited time in these studies. Future animal models should reproduce the comorbidities, risk factors for multiorgan failure, and prolonged critical illness common in patients with ARDS.

Many of the treatments tested may simply not be efficacious, and for some others, the side effects may outweigh the benefits. However, while benefit has been demonstrated in numerous preclinical studies for many candidate therapies, most have failed to translate to improved outcomes for patients in randomized clinical trials, suggesting that either the experimental models poorly represent the clinical syndrome or that the appropriate subset of patients to target with the novel therapies has not been correctly identified. Because ARDS mortality remains high, current initiatives also include primary prevention, with a key challenge being to identify at-risk patients

in whom ARDS is likely to develop and who would benefit if ARDS were prevented. No preventive pharmacologic strategy has proven effective to date, and although clinical scores can identify patients who are more likely to develop ARDS, biomarkers may improve the predictive value of clinical-only scores in select at-risk populations.

The recognition of ARDS phenotypes and endotypes

There has only been recent recognition of the clinical and biological heterogeneity within ARDS, which reflects an incomplete understanding of ARDS biology. Although it was previously subdivided on the basis of clinical risk factors or by a direct versus indirect cause of lung injury, consensus does not currently exist on the most appropriate approach to reduce ARDS hetero-geneity. In ARDS, recent evidence suggest distinct phenotypes (on the basis of clinical/biochemical variables, natural history, disease manifestation,
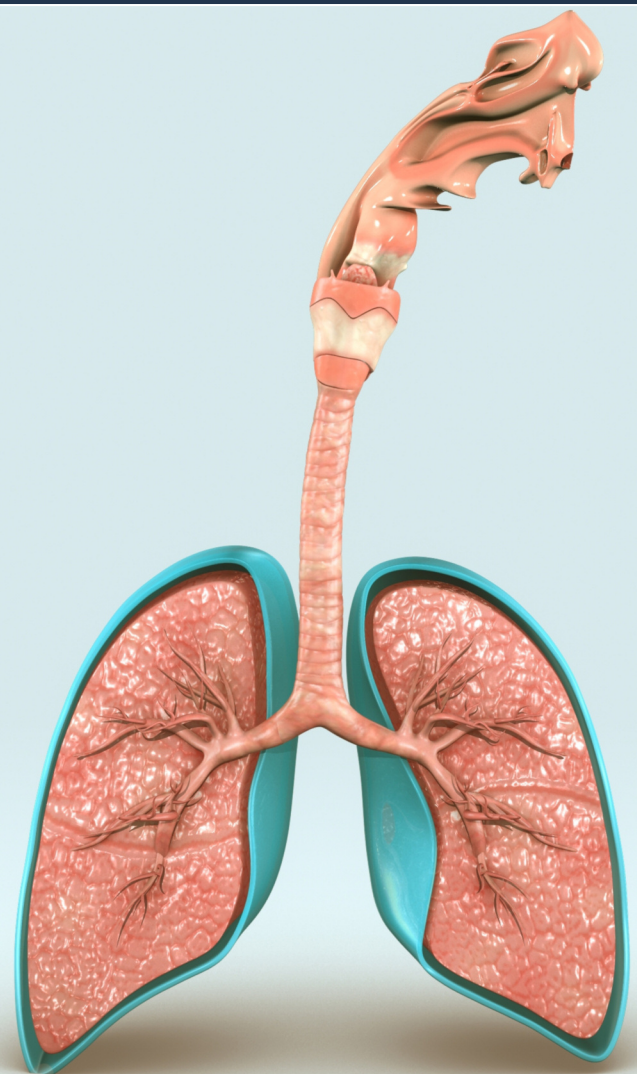
and/or response to treatment without any implication about mechanism) and endotypes (defined by a distinct functional or pathobiological mechanism) for ARDS. Phenotypes that have been reported to date may be classified by severity, biology (e.g. hyperinflammatory versus hypo-inflammatory phenotypes), etiology, timing, lung morphology, or lung physiological or mechanical properties.

For example, a working hypothesis has been that elevated plasma sRAGE (soluble receptor for advanced glycation end-products) could reflect the severity of alveolar epithelial injury in the lungs from patients with ARDS. This theory is supported by recent studies, including evidence in the *ex vivo* human lung. It has been demonstrated in ARDS that alveolar fluid clearance (AFC, i.e.

the resolution of alveolar edema) is impaired when sRAGE is elevated in the alveolar fluid or plasma. Interestingly, a phenotype of nonfocal lung morphology (or nonfocal morphotype) is associated with an endotype of more severely impaired AFC, thus providing the first evidence of distinct functional patterns between focal and nonfocal ARDS. As RAGE pathway may play a major role in the mechanisms leading to AFC and its regulation (even though its precise roles are still under investigation), a growing body of evidence now supports an association between RAGE pathway, impaired AFC and ARDS morphotypes. This may fill a gap in the full recognition of a phenotype of lung morphology that could be linked to an endotype of impaired AFC and an activated RAGE pathway. Of note, such a hypothesis on endotypes could be of

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particular importance because both impaired AFC and higher plasma levels of sRAGE have been associated with outcome, because the biological plausibility is high, and it is inherent in the process of ARDS evolution.

Indeed, the current definition of ARDS, based on clinical and radiographic data, has probably hindered the identification of targeted therapies used to manipulate select biological mechanisms underlying ARDS. Although we have long been able to identify subtypes within ARDS (i.e., subsets of patients that do not necessarily imply differences in function, biology, or observable characteristics) that confer different prognoses, the novelty is that we are now able to identify phenotypes and endotypes that may confer different response to therapy.

Opportunities for precision medicine in ARDS

Precision (or personalized) medicine, i.e. the concept that everyone has a unique response to disease susceptibility and drug metabolism, is far from being a revolutionary concept. More than 2,000 years ago, Hippocrates emphasized the importance of a personalized approach to medicine: "*It is far more important to know what person the disease has than what disease the person has*" (Hippocrates (460 BC-370 BC)). Because a growing body of literature now supports the identification of various forms of ARDS with potential differences regarding their management, response to therapeutic interventions or prognosis, the next step will be to implement and evaluate the concept of precision medicine to inform therapeutic approach and tailor treatment and prevention strategies to individual patients with ARDS.

However, most pieces of evidence supporting such phenotypes or endotypes have been generated by retrospective, small-sized and/or unreplicated studies, and more work is needed from us to refine and validate known phenotypes/endotypes, as well as to discover new ones. In addition, the question of clinical impact remains open for most proposed ARDS phenotypes/endotypes and future studies are warranted to confirm the full potential of precision medicine for ARDS, i.e. the promise to deliver the right (targeted) treatment at the right time and to the right person.

Main challenges that hamper the implementation of precision medicine in critical care include insufficient evidence generation, infrastructure challenges, and how to efficiently handle and analyze high throughput data. Although randomized clinical trials are still the gold standard for evidence generation, an emerging approach is to collect data as part of ongoing clinical care in order to generate evidence for patient and economic outcomes. Some of the most important
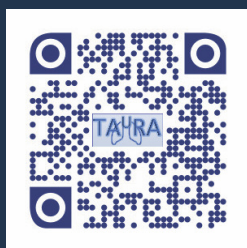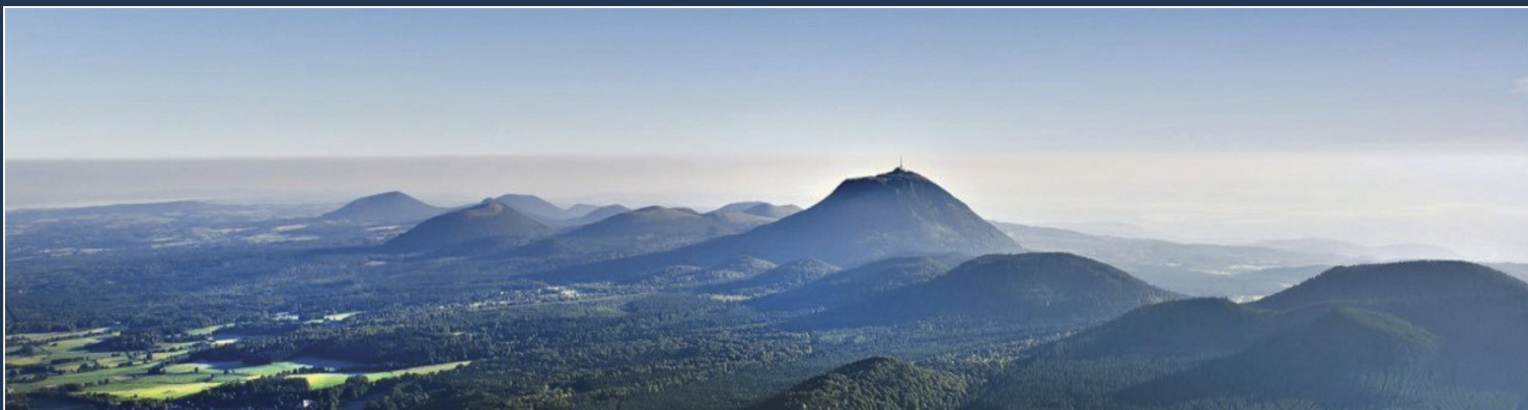
benefits of precision medicine may involve identifying healthy individuals at elevated risk of disease, to facilitate the implementation of targeted preventive therapies. Depending on the disease, a precision medicine innovation that accurately identifies at-risk patients and is coupled to an intervention which reduces disease incidence by 10% could generate hundreds of billions of dollars in value. However, diagnostic tests have not flourished as rapidly as expected, due, in part, to a challenging economic environment for innovators. To realize the promise of precision medicine, it is now crucial to develop evidence of its benefit, accelerate clinical data integration and assessment, and promote the integration of molecular guidance into care. Advanced study designs need to be applied to precision medicine for ARDS. Firstly, the translation of basic research findings into clinical practice should be improved using experimentation that is most capable of optimally modeling the heterogeneity and complexity of ARDS. Therefore, ideally, specific endotypes described in patients with ARDS should be reproduced in future experimental models. There are several other hurdles to effective clinical trial designs for ARDS, including cost. The need for large-scale trials with many participating sites poses logistical challenges and requires adequate research infrastructure investment. Therefore, mechanistic physiological and biological data should be collected during the trials, whenever possible, to evaluate not just whether a treatment is beneficial, but why and for whom.

What steps are needed to move precision medicine for ARDS closer to reality? First, a deeper understanding of the clinical and biological heterogeneity within the syndrome is needed. Large, international, multicenter well-character-ized patient cohorts, with thoughtfully planned data collection and biosample repositories, are required to further refine and validate known phenotypes/endotypes and to identify novel patient subgroups that may not necessarily correspond to our presuppositions about ARDS heterogeneity. Such studies are needed to test prospectively the logistics of incorporating clinical, imaging, and biologic measurements that best identifies subgroups for trial enrichment, balancing needs for feasibility and generalizability. Second, the translation of basic research findings into clinical practice should be improved using experimentation that is most capable of optimally modeling the heterogeneity and complexity of ARDS. Therefore, ideally, specific endotypes described in patients should be reproduced in future experimental models, and targeted therapies should be tested in experimental studies that are most likely to model specific disrupted function or biology. Finally, investment in the development of point-of-care tests is needed with the objective of being able to rapidly assess endotypes at the bedside and the goals of testing more personalized approaches to managing patients with ARDS and to ultimately improve clinical outcome.

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