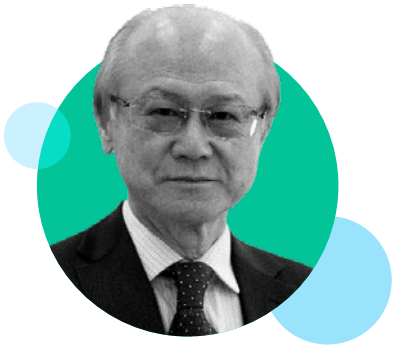
Interviews

EMJ is delighted to share exclusive interviews with three leading voices in the field of respiratory medicine. Kian Fan Chung discusses biomarker-driven precision medicine, corticosteroid resistance, and digital tools in asthma care. Lucilla Piccari highlights advances in understanding and managing pulmonary hypertension associated with lung disease. Sir Peter Barnes reflects on breakthroughs in asthma and COPD, from biomarkers to senotherapies.



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Q1 As co-leader of the European Unbiased BIOmarkers in PREDiction of respiratory disease outcomes (U-BIOPRED) Consortium, you have been instrumental in redefining how we classify severe asthma. What are the most important biomarker discoveries to come out of this project, and how are they shaping the treatment of severe asthma?

The U-BIOPRED Consortium cohort database has now been in existence for the past 10 years.[1] Various analyses of the study cohort continue to be published from this dataset, which remains an important repository of *omics* data on severe asthma and has been instrumental in redefining the classification of the condition.

Together with work coming from places such as the USA Severe Asthma Research Program (SARP), this has allowed us, for the first time, to define the various phenotypes. Extensive *omics* data can provide a more granular definition of molecular phenotypes or endotypes of severe asthma. These approaches have confirmed the heterogeneity of the immune and inflammatory pathways that drive asthma at an individual level, emphasising that this condition is not a black-and-white situation when considering Type 2 (eosinophilic) versus non-Type 2 (non-eosinophilic) inflammation or immune responses.

> **Extensive omics data can provide a more granular definition of molecular phenotypes or endotypes of severe asthma**

U-BIOPRED has been instrumental in initiating the application of precision medicine in asthma, though this has not yet reached the clinic. As an example of the approach that we have taken in our work, starting with sputum *omics* data, we first defined groups of eosinophilic or neutrophilic inflammatory phenotypes based on transcriptomics or proteomics data. We subsequently integrated various *omics* platforms, including transcriptomics, proteomics, and metagenomics, to obtain further granularity of these endotypes. This integrative *omics* approach to dissecting severe asthma is, in fact, one of the great achievements of U-BIOPRED, made possible by a collaborative academic-industrial public-private partnership,[2] as well as

the decision to have a central repository for all data and biobanking.

Another concept that has come out of U-BIOPRED is that, despite the description of various endotypes using this integrative approach, it is unwise to view asthma in terms of definite boxes. For instance, there is a prevalent idea in the clinic that asthma is either a Type 2-high or a Type 2-low condition. Using techniques that allow us to determine the extent of involvement of particular pathways or cells, it is clear that each of these pathways overlaps between any defined endotypes. In addition, we now have evidence that many interactions occur between these different immune and inflammatory cells or pathways that could determine particular clinical aspects of the disease.

Are these new findings shaping the treatment of severe asthma? We very much hope they will.

Real hard precision medicine has yet to reach the clinic. We need to validate and confirm all these findings, and though this has been done to some extent, we need to start applying it to severe asthma. With the increasing granularity of endotypes, we need more specific biomarkers with greater precision to define the driving pathways. This means using biomarkers that will transcend measurements dependent on just a number of given circulating cells. There is no reason why we cannot introduce these findings into the clinic now.

Q2 The issue of corticosteroid resistance in asthma and COPD remains a major clinical challenge. What mechanisms do you believe are most critical in this resistance, and how close are we to overcoming it with new therapies?

The issue of corticosteroid resistance in asthma has been a major challenge, and there continues to be interest in understanding the underlying causes in order to find ways of reversing it. However, the introduction of Type 2 biologic therapies has likely reversed corticosteroid resistance in eosinophilic asthma.

A wide variety of mechanisms have been implicated, starting with the reduced expression of the transducing glucocorticoid receptor (GR), GRα, and the increase in non-transducing GR, GRβ, which acts as an antagonist of GRα. We and others have also provided evidence that cytokines of the Type 2 pathway, such as IL-4 and IL-13, were able to interfere with GR binding affinity, and that for IL-4, this occurs through the phosphorylation of GR, particularly by p38 mitogen-activated protein kinase (MAPK).

Corticosteroid resistance in neutrophilic asthma has also been described, implicating the role of T helper 17 cells associated with PI3K and histone deacetylase 2

(HDAC2) mechanisms. Chlamydia or *Haemophilus influenzae* infections have also been implicated in this.

Finally, oxidative stress remains a very important mechanism, particularly in relation to the corticosteroid resistance we see in COPD.

The introduction of biologic therapies, such as anti-IL-5, anti-IL-5 receptor α (IL-5Rα), and anti-IL-4Rα antibodies, not only reduced or abolished asthma exacerbations in those with high blood eosinophil counts and/or high fractional exhaled nitric oxide (FeNO), but has also allowed a reduction in maintenance oral corticosteroid therapy while maintaining improvement in asthma. The interpretation of this effect is that the patients' response to corticosteroids has been restored through the inhibition of these Type 2 cytokines, particularly IL-4 and IL-13, which were implicated in the induction of corticosteroid resistance many years ago.

It would be interesting to see whether these biologic treatments would be effective in reversing corticosteroid resistance in neutrophilic asthma or COPD, or whether targeting certain non-Type 2 targets would be successful.

Q3 Your research touches on the impact of environmental pollutants and nanoparticles on respiratory health. How should clinicians be thinking about environmental exposure when diagnosing and managing chronic airway diseases?

There is little doubt that environmental pollutants represent one of the biggest threats to human health, particularly respiratory health. The lungs are the site of entry for these toxic particles and gases, and we all breathe up to 30,000 times every day. This threat will be increased by climate change, which is already impacting the whole ecosystem.

My work in this field has been about trying to understand the impact of these toxic particles and gases, both at the cellular and the whole-person level. At the cellular level of the airway epithelium, it has been fascinating to understand how these nanoparticles of pollution interact with the cell membrane to induce the production of oxygen radicals, which have damaging properties from which the whole cascade of inflammation and tissue damage is initiated. At the whole person level, my work has focused on the extent to which real-life exposures affect the cardiovascular–respiratory system in order to seek any early warning signs that environmental pollution is starting to cause a problem. I am hoping that this work will be helpful for the community and for patients, providing guidance on how to mitigate the effects of environmental pollutants on their health.

It is clear in my mind that clinicians play a key frontline role in thinking about environmental pollution in the clinic when diagnosing and managing patients, particularly those with respiratory and/or cardiovascular diseases, because

it has an impact on the lungs and the heart; these patients are more susceptible to the detrimental effects of pollution than others.

However, there are some issues here, as many clinicians feel that they are not knowledgeable enough about the effects of pollution. They are unsure what advice to give patients regarding avoidance and how to determine the contribution of pollution to their medical conditions. These hurdles can be overcome with the inclusion of pollution and climate change as topics of continuing medical education. This should be essential for all clinicians and should include theoretical and practical aspects. I believe that the European Respiratory Society (ERS) could also play a role in this regard.

> **There has been a lot of progress in our understanding of chronic cough, which is defined as a cough that has lasted for >8 weeks**

Advising patients on how to reduce their exposure is an active area of research at the moment, with ongoing investigations into the need for personal monitoring, the value of protective measures, and the contribution of diet, lifestyle, and various medicines. This means that all clinicians need to keep abreast of any developments happening.

Finally, I would say that clinicians should also play a role in advocating for the right of every person and patient to breathe clean air, because they can see how their patients are directly affected by pollution. There will be a session at the ERS Congress in Amsterdam, the Netherlands, on this topic: 'Patients and pollution: the science and best practices for care providers' advice'.

Q4 You've also been at the forefront of developing novel cough suppressants and exploring the neural pathways behind cough hypersensitivity. How is this changing the way that we understand and treat chronic cough?

There has been a lot of progress in our understanding of chronic cough, which is defined as a cough that has lasted for > 8 weeks. It is a worldwide problem, with up to 5–10% of the adult population in many countries affected by chronic cough. The realisation that many patients with chronic cough do not have any conditions that we associate with causing cough led to the concept of unexplained or refractory chronic cough (UCC/RCC). This was contrary to the belief held by some that a chronic cough is highly treatable if the cause is diagnosed and treated.

So far, a large proportion of people who have UCC/RCC attend cough clinics. The recognition of UCC/RCC has led to the realisation that this condition is underpinned by cough hypersensitivity, which has been defined as a clinical syndrome characterised by troublesome coughing that is often triggered by low levels of thermal, mechanical, or chemical exposure.[3] This concept has been around for a while, since it was known that these patients were more sensitive to chemical tussive agents such as citric acid or capsaicin, which is the extract from chillies that causes a burning sensation in the throat upon ingestion or inhalation.

This realisation around UCC/RCC has received increasing scientific support, with a greater understanding of the underlying mechanisms. These involve peripheral neuroinflammatory mechanisms in the upper airways affecting cough channels and receptors, and central neural pathways in the brain stem, midbrain, and cerebrum, which are assessed by brain MRI techniques.

From this understanding, the development of specific targeted therapies has ensued; for example, cough sensory neuron-targeting P2X3 receptor antagonists, the first of which, gefapixant, has shown efficacy in improving cough in UCC/RCC.

Another important aspect of chronic cough and cough hypersensitivity that is currently gaining attention is the objective measurements of cough. The current advent of automatic analysis of cough events using digital tools and machine learning, allowing for continuous unobtrusive recordings over long periods of time, will provide some more information on the basis and mechanisms underlying cough hypersensitivity at an individual level.

These important advances have pushed forward the consideration that chronic cough is a distinct condition with specific underlying mechanisms and new targeted therapies that justify the label of a disease. This reclassification of people with chronic cough will have substantial positive implications for the patient, improving our clinical approach, shaping healthcare policy, and advancing research outcomes

to improve the care of cough hypersensitivity. There will be a symposium on 'Cough phenotyping: from the clinic to treatment' on the 29th of September 2025, at the ERS Congress in Amsterdam, the Netherlands.

Q5 Can you tell us more about the myAirCoach project? How do you see mobile-health (mHealth) tools transforming personalised care in asthma management?

The myAirCoach[4] study was a project funded by EU Horizon 2020 and run by 12 European partners to develop an mHealth system on an app-based platform. The aim was for the system to facilitate data collection and asthma self-management through the use of home monitoring and the prediction of asthma exacerbation occurrences. It was one of the earlier pioneering studies that started to look at mHealth systems with the aim of improving the self-management of asthma through the collection of data, specifically regarding asthma control, inhalation technique, biomarker measures, and environmental exposure. This data would give the patient a wider insight into their condition and how it's affected by their environment and behaviour.

MyAirCoach first reported that compliance with measuring domiciliary spirometry and FeNO varied widely among patients, even in a research study involving a group of people with moderate-to-severe asthma. Despite this, we reported that changes in FeNO and forced expiratory volume were associated with asthma exacerbations and asthma control, making these measurements clinically valuable in determining asthma control and exacerbation onset. In a subsequent study,[4] we went on to show that mHealth-supported self-management aided by the myAirCoach system was effective in clinically improving asthma control, exacerbation rates, and quality of life. In addition, end-users of this mHealth platform reported generally positive attitudes towards the system.

Since then, there have been improvements in mobile technologies, from healthcare home-monitoring systems to wearable devices. Several larger studies, similar to the type conducted by myAirCoach, have shown the benefit of this mHealth approach in both children and adults with asthma, resulting in improvements in adherence and a reduction in exacerbations, emergency department visits, and the use of rescue medication.

In addition, machine learning has more recently been used to process large amounts of data that have been collected to identify patterns so that tools or techniques can learn how to do a given task. For example, these tools could be used to predict when an exacerbation of asthma might happen based on previous data. Furthermore, the development of wearable devices that measure a wide range of specific parameters relating to asthma (e.g., detection of wheeze, dyspnoea, and cough) will facilitate the collection of all the necessary information.

I believe that the future of asthma management will be determined by the judicious use of home-based self-monitoring, combining

mHealth with machine learning. However, there will need to be validation of these new digital technologies and approaches in clinical trials and studies. This will emerge as a valuable means of delivering medical care to patients suffering from asthma.

Q6 Looking ahead, what do you believe will be the key breakthroughs in precision medicine for asthma and COPD over the next 5–10 years?

I think that bioinformatic analysis, coupled with machine learning, will improve the clustering of molecular phenotypes or endotypes of asthma with more accurate biomarkers, which are essential tools needed for the practice of precision medicine in the clinic. There is already great interest in building up techniques in multi-omics integration, which may provide more granularity of the phenotype. In addition, we now have patients undergoing biologic therapies. This will allow us to understand the perturbations of inflammatory and immunological pathways, induced by blocking a single Type 2 pathway, that link up to biological and therapeutic responses. There is also the possibility of predicting which drugs could be used in specific endotypes. The ultimate aim of precision medicine is to give the right treatments to the right patient at the right time.

Finally, the major breakthrough will be the application of all these approaches to precision medicine in the clinic. Currently, the use of blood eosinophil count as the main biomarker in clinics is not accurate enough to predict who will respond to existing biologic treatments. Therefore, we need to use more refined biomarkers for a wider variety of targets. I hope that this occurs soon, as we can then include the use of biologic therapies against so-called non-Type 2 targets. This will also apply to COPD.

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