3TR

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3TR: a pan-European cross-disease research consortium aimed at improving personalised biological treatment of asthma and COPD

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Shareable abstract (@ERSpublications)
3TR, the largest IMI consortium ever in immune diseases, brings clinical researchers and scientists from several disease areas together, in an endeavour to increase the clinical impact of targeted immune-mediated therapies, including asthma and COPD https://bit.ly/3kPq0xI

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3TR: focusing on current challenges in the management of asthma and COPD

The 3TR (Taxonomy, Treatments, Targets and Remission) consortium is the largest IMI (Innovative Medicine Initiative) project ever started in the field of immune diseases (https://3tr-imi.eu/). 3TR is unique in bringing several medical specialties, encompassing respiratory medicine, rheumatology, neurology and gastroenterology, together, to study disease mechanisms across seven disease entities: asthma, COPD,

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systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, ulcerative colitis and Crohn's disease.

Asthma and COPD are some of the most common chronic diseases; there are approximately 600 million people with asthma and 400 million with COPD worldwide [1, 2], with COPD being the third leading cause of death worldwide [2].

Management options of both asthma and COPD have advanced significantly, with both new inhaler formulation and biological treatments that target specific disease pathways transforming treatment options for patients with severe asthma [3]. However, these treatments do not completely abolish all exacerbations or symptoms, they do not achieve complete disease control and they do not cure the disease. In addition, they are directed against type 2 inflammation, but no treatments are so far available for patients without type 2, or for patients with COPD. Therefore, there is a further need for improved targeting of biological (and other) treatments.

A range of biological treatments developed for asthma have been tested in COPD, with limited efficacy; a clearer understanding of immunological disease drivers in COPD is necessary. Although there are commonalities between asthma and COPD, such as eosinophilia being a predictor of exacerbations and responsiveness to inhaled corticosteroids, there are also clear differences, illustrated by the modest effects of blocking IL-5 in COPD patients with high levels of eosinophils, compared to their marked pronounced beneficial effects in severe eosinophilic asthma [4, 5].

Both asthma and COPD are chronic conditions, which require continuous, possibly life-long, treatment. No disease-modifying treatments exist at this point (except allergen immunotherapy in very selected cases [6]), and there is a need for increasing treatment ambitions, to aim for remission of disease [7]. The ambition of 3TR is to move the field of immune-modifying treatments forward in a pan-European, concerted effort by combining the forces of clinical researchers and scientists in a 7-year collaborative effort.

Specifically, the focus of the 3TR consortium is to address:

- What specifically constitutes a response or non-response to biological therapies in asthma and COPD?
- What are the underlying immunological mechanisms that explain the reasons for response *versus* non-response? And for super-response *versus* response?
- Can we identify biomarker profiles predicting response or non-response by combining repeated bio-sampling from multiple compartments with advanced multi-omics methods in patients treated with biologics?
- What can we learn from comparing different immune-mediated diseases across different organs and systems?
- How can we translate these insights into better approaches for precision medicine for asthma and COPD, such as the introduction of new biomarkers?

The consortium involves a collaboration between academic researchers, patients and the pharmaceutical industry.

Potentials for developing solutions

The most significant advances in immune-targeted therapies have occurred in asthma, potentially ultimately paving the way towards such therapies for COPD. At present, the advent of biological treatments for severe asthma represents a unique opportunity to further unravel the pathogenesis of obstructive airway diseases. Specifically, a lack of response to biologics, as well as a super-response, may provide important insight into pivotal immunological mechanisms and pave the way towards more effective interventions.

As a first important focus, we need to have a clearer understanding and agreed concept of what qualifies as a response: a number of response outcomes are of importance, including patient-reported outcomes, exacerbation rates and lung function, and prevention of disease progression, which should be achieved with minimal treatment side effects. Currently, biomarkers such as eosinophils and exhaled nitric oxide fraction may be used to predict a response to T2 biologics, but more alternatives and especially non-T2 markers are needed. Different definitions of response and non-response have been proposed [8, 9], but it remains uncertain how specific response profiles translate into long-term outcomes: is complete abrogation of exacerbations necessary for patients to achieve long-term complete clinical control of their disease? Is complete suppression of disease signatures, such as all T2 biomarkers, important?

A second important focus is to link specific immune mechanisms to either a non-response or a "super-response" (*i.e.* above what could be expected based on results from phase 3 trials), or to "clinical remission" to identify future treatment targets. Specifically, a future ambition is to aim for remission of disease as a management goal: achieving long-term complete control and preventing progression of the disease [7]. Within rheumatology, treating with the aim to achieve complete clinical control has translated into better remission rates [10, 11]. A similar effect may be seen in severe asthma where a complete control of both symptoms and airway inflammation could potentially improve the likelihood of long-term control. By furthering our understanding of the immunological mechanisms driving eosinophilic COPD, we may also move towards better management strategies for inducing long-term stability and prevention of progression in patients with COPD. A unique aspect of 3TR is precisely the cross-disease focus that enables evaluation of immunological pathways associated with disease controls and remission, irrespective of diagnostic label.

A third focus of 3TR is the potential of advanced immunological analysis methods: molecular profiling and integration of multi-omics data may stratify individuals with clinically heterogeneous diseases to identify the molecular basis of their pathogenesis and potential new biomarkers. Through large-scale research consortia such as U-BIOPRED, we have achieved important insights into the heterogeneity of severe asthma that are likely to direct the way towards better management strategies [12, 13]. However, most existing studies have so far been cross-sectional or without specific immune-modifying interventions.

With the advent of a range of targeted biological treatments for treating severe asthma, we are now in a position to study the immunological effects of blocking individual immune pathways, such as IgE, IL-5 and IL-4/13, and the upstream TSLP and IL33 pathways, to gain better insights into the pathogenetic drivers of severe asthma. This mandates longitudinal studies with biosampling "real-life" patients treated with biologics.

For COPD, studies targeting the same pathways will enable us to compare mechanisms across asthma and COPD, and to move forward our understanding of similarities and dissimilarities between the two conditions. As the effect of targeted monoclonal antibodies has been less convincing in COPD in general, there is an urgent the need to determine the mechanisms involved in a clinical response. By applying advanced immunological analyses to samples obtained before and after specific antibody treatments, and comparing responders to non-responders, we may obtain a clearer understanding of key pathogenic mechanisms, to aid in developing more effective therapies.

How to unleash these potentials: 3TR

The strategy of 3TR combines five key elements: 1) the expertise of world-leading experts, clinical researchers and translational scientists in each disease area, with pharmaceutical companies, patient organisations, and small- and medium-sized enterprises; 2) prospective collection of multiple samples from both diseased tissue and blood; 3) use of samples from existing studies; 4) advanced state-of-the-art multi-omics analysis; and, finally, 5) use of a "carousel model" to boost the efficient generation of evidence throughout the 7-year duration of 3TR, allowing a simultaneous and continuous process of analysing existing data and samples, alongside collecting new samples (figure 1).

As a primary step, to define therapeutic response and non-response and to allow comparisons across different studies, it is necessary to study biomarkers and immunological mechanisms related to different responder profiles. A key aim of the 3TR Asthma and COPD Work Package (3TR WP8) is, therefore, to map and define outcome measures for documenting therapeutic response. These outcomes will take into consideration the opinions of the three stakeholders of 3TR: patients (may rather focus on the ability to lead a normal daily life), clinicians (likely to focus on objective outcomes) and healthcare funders (likely to focus on healthcare costs). Ultimately, criteria for non-response and response for use in future trials will be defined in clinical practice.

In order to validate biomarkers predicting response, existing studies will be used in parallel with introduction of *de novo* studies, in the carousel model proposed by 3TR WP8. Within the respiratory field, a number of phase 2 and 3 trials are ongoing or will be soon started, examining the effects of monoclonal antibody treatment in patients with asthma and COPD. The participation of industry partners in 3TR represents a forceful opportunity to study and compare the effects of targeting individual immune pathways in asthma and COPD. Simultaneously, large multicentre academia-led trials are studying parallel questions on the effects of biologics, such as the Predictumab trial comparing the effect of anti-IgE to anti-IL5 in severe asthma patients eligible for both treatments, or the BenRex trial, studying exacerbations of severe asthma during treatment with benralizumab. Observations in these studies will be combined with those in

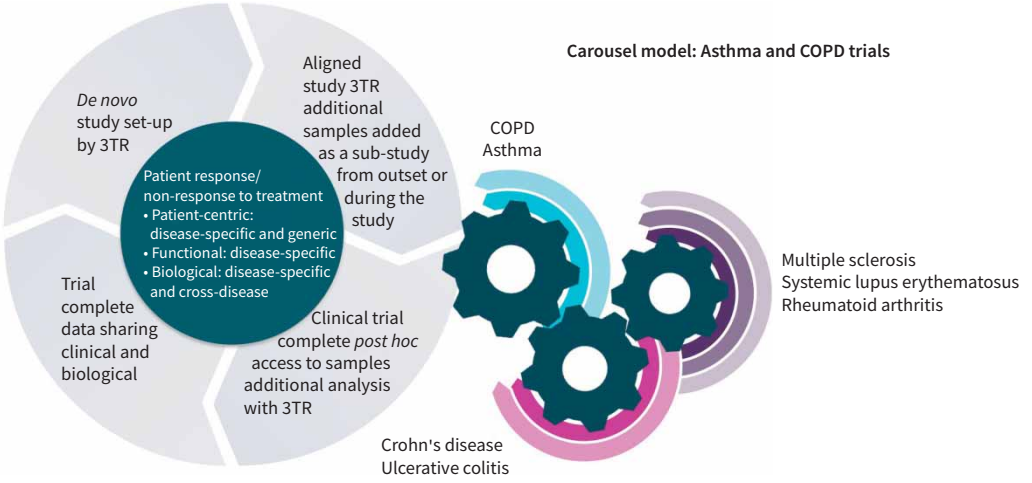

FIGURE 1 The 3TR carousel model: samples obtained from existing studies are analysed in parallel with prospective sampling in aligned and *de novo* studies, to achieve effective generation of data throughout the 7-year duration of the 3TR programme.

the SoMOSA (Study of Mechanisms of action of Omalizumab in Severe Asthma), identifying biomarkers predicting reductions in exacerbation rates and use of oral corticosteroids.

WP8 will set up a trial platform to enable cross-study analyses, providing an overview of studies with a catalogue of existing and planned studies and enabling cross-study analyses by defining common standard operating procedures (SOPs) for setting up *de novo* cohorts, outlining study visits, clinical assessments, sample types and sample processing.

Additionally, WP8 will set up a pan-European prospective cohort, to assess and compare responses to different biological treatments in a large real-life population of patients with severe asthma, including both adults and children. By comparing responders and non-responders, the 3TR Asthma Biologics Cohort study (3TR-ABC) will describe immunological mechanisms related to response profiles and identify biomarkers for predicting response, as well as possible future treatment targets (figure 2).

As biological therapies are not yet approved for COPD, samples from pharmaceutical trials will be used to investigate immune mechanisms involved in response *versus* non-response. The 3TR-ABC study will be followed by the establishment of a cohort of COPD patients, which may ultimately include patients commenced on a biological treatment, if such treatments are approved for clinical use.

Obtaining high-quality airway samples will be key to successful multi-omics analysis, highlighted by the experience from previous translational studies such as U-BIOPRED, in which a significant proportion of sputum samples were not of adequate quality for performing omics analysis [12]. A catalogue of SOPs describing the processing of bio-samples will be assembled, combining SOPS from previous studies with novel sampling methods and protocol optimisation.

Finally, by including assessment of other immune-mediated diseases, the 3TR-ABC study enables exploration of shared immune pathways across different diseases, providing new insights into asthma and COPD as systemic diseases, and their potential endotypic connections with other non-respiratory immune diseases.

Perspectives

The insights into immune disease mechanisms in asthma and COPD provided by 3TR may uncover future treatment targets and identify relevant patient populations to address such targets. Furthermore, the validation of biomarkers to guide management choices is increasingly important, considering the increasing numbers of biologics available. Finally, as we move towards higher ambitions for treatment outcomes in asthma and COPD, the work undertaken by 3TR will provide an important basis for future studies on disease modification.

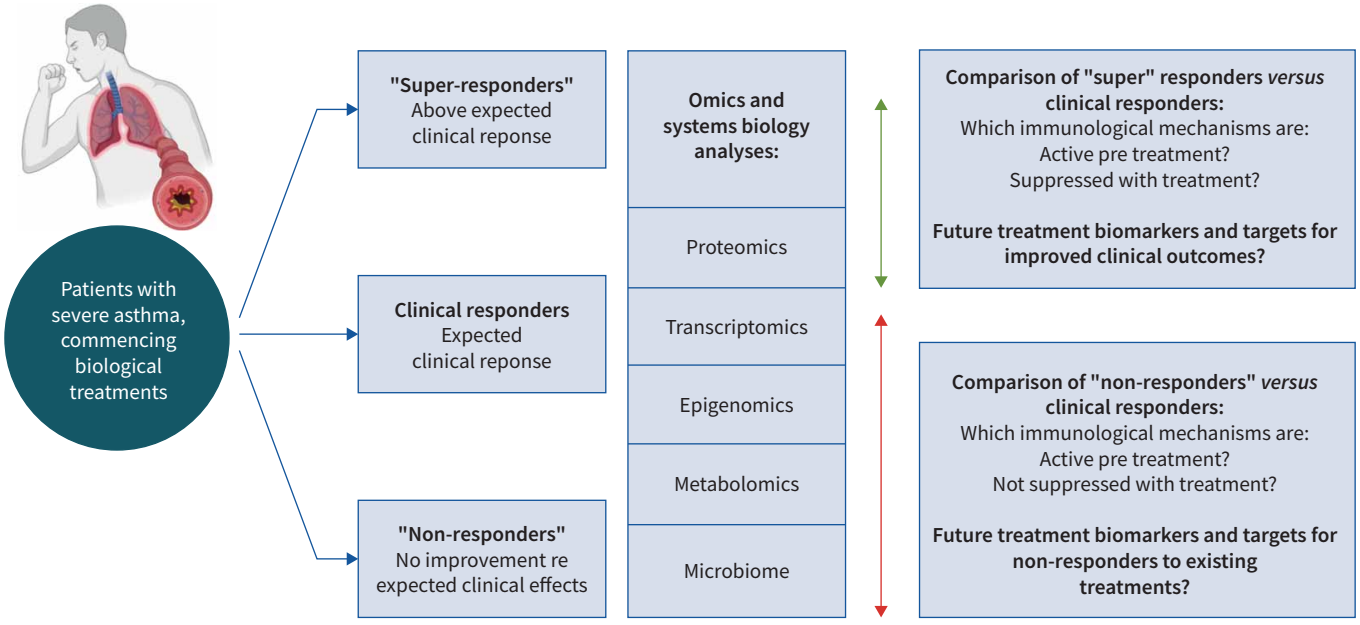

FIGURE 2 The 3TR Asthma Biologics Study (3TR-ABC): identifying novel treatment targets in severe asthma through the response to biological therapy.

In conclusion, the 3TR research consortium brings together European, patients, pharma and other stakeholders or experts in different medical specialties to elucidate disease mechanisms in this unique era of targeted biologics, unleashing strong potentials ultimately to move towards more ambitious treatment goals for patients with asthma and COPD through precision medicine in our field of interest and, potentially, also in other medical subspecialties.

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