Asthma innovations from the first International Collaborative Asthma Network forum

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Shareable abstract (@ERSpublications)
Understanding asthma mechanisms beyond T2 inflammation is vital. At the first ICAN forum, innovative asthma research on non-T2 inflammation was shared, providing a foundation for future sharing and prioritisation of asthma research and collaboration.
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Abstract

Background Many patients have uncontrolled asthma despite available treatments. Most of the new asthma therapies have focused on type 2 (T2) inflammation, leaving an unmet need for innovative research into mechanisms of asthma beyond T2 and immunity. An international group of investigators developed the International Collaborative Asthma Network (ICAN) with the goal of sharing innovative research on disease mechanisms, developing new technologies and therapies, organising pilot studies and engaging early-stage career investigators from across the world. This report describes the purpose, development and outcomes of the first ICAN forum.

Methods Abstracts were solicited from interdisciplinary early-stage career investigators with innovative ideas beyond T2 inflammation for asthma and were selected for presentation at the forum. Breakout sessions were conducted to discuss innovation, collaboration and research translation.

Results The abstracts were categorised into: 1) general omics and big data analysis; 2) lung–brain axis and airway neurology; 3) sex differences; 4) paediatric asthma; 5) new therapeutic targets inspired by airway epithelial biology; 6) new therapeutics targeting airway and circulating immune mediators; and 7) lung anatomy, physiology and imaging. Discussions revealed that research groups are looking for opportunities to further their findings using larger scale collaboration and the ability to translate their *in vitro* findings into clinical treatment.

Conclusions Through ICAN, teams that included interdisciplinary early-stage career investigators discussed innovation, collaboration and translation in asthma and severe asthma research. With a combination of fresh ideas and energetic, collaborative, global participation, ICAN has laid a firm foundation and model for future collaborative global asthma research.

Introduction

Asthma is a common disease that affects males and females of all ages and races. In 2019, an estimated 262 million people worldwide had asthma [1]. There has been progress in treatments for asthma in the last

four decades. Inhaled corticosteroids reduce the airway inflammation underlying the manifestations of asthma, improve lung function, and reduce airway hyperresponsiveness, frequency of exacerbations and daily symptoms [2–4]. Their widespread use (with or without long-acting β-agonists) has resulted in a substantial decline in asthma-related mortality and hospitalisations [5–8]. Other treatments include leukotriene receptor antagonists, muscarinic antagonists and most recently, biologics targeting important components of inflammation, specifically immunoglobulin E (IgE) and mediators of type 2 (T2) inflammation (*i.e.* interleukin (IL)-4 receptor subunit, IL-5, IL-5 receptor, thymic stromal lymphopoietin). T2 inflammation has a key role in asthma pathophysiology and increases susceptibility to exacerbations [9].

Despite the available treatments, many patients still have uncontrolled asthma. In an analysis of 2014–2017 data from an international registry of 4990 patients with severe asthma, country-specific results indicated that in 37–88% of patients it was uncontrolled [10]. Lack of asthma control in some can be attributed, in part, to modifiable factors, such as nonadherence to treatment and poor inhaler technique, but uncontrolled asthma also occurs in patients taking their medications as prescribed [11]. A substantial proportion of patients with asthma do not consistently express a T2-high phenotype and do not, therefore, benefit from the advances in T2 biologics, leaving a major unmet need for additional therapies [12]. Moreover, current treatments are life-long, and there is no mucosal healing as is found in other chronic inflammatory diseases.

A heavy clinical burden associated with asthma still exists, including exacerbations leading to emergency department visits, hospitalisations and intensive care admissions [13, 14]. In 2019, asthma was responsible for 461 000 deaths globally [1]. In addition, surveys conducted within the last few years indicate that, even in the age of biologics, patients frequently report their asthma interferes with daily activities, work or school, and sleep [15, 16]. Clearly there is a continued need for innovative research into additional mechanisms of asthma beyond T2 inflammation and interventions to enable the development of new therapeutic targets. In addition, there remains a need to improve asthma diagnosis to reduce under- and overdiagnosis that results in patient harm and excess clinical and economic burdens.

To address the need for innovation and for collaboration globally, investigators, primarily from the USA and UK, have met annually at the European Respiratory Society and American Thoracic Society (ATS) meetings over the past few years to foster collaborations. These meetings generated enthusiasm for ongoing dialogue and interest in planning for a more formal gathering focused on advancing severe asthma research. This led to establishing the International Collaborative Asthma Network (ICAN) that aimed to promote innovative asthma research, particularly in severe asthma, to bridge innovative research outcomes and common data that can be translated into improved patient diagnosis or treatment. The overarching themes of ICAN are innovation, collaboration and translation. ICAN hosted an international interdisciplinary early-stage career researchers' forum in May 2022, immediately prior to the ATS Annual Meeting. The goals of this gathering were to share innovative findings on disease mechanisms, to develop new asthma technologies and therapies, to organise pilot studies and to engage early-stage career investigators. This report describes the purpose, development, outcomes and overall themes of the first ICAN forum.

Methods

Development of ICAN

Organising committee

The ICAN organising committee, which included severe asthma experts from the USA and UK, was convened by the Indiana University Paediatric Translational Research Programme, Asthma+Lung UK (since then merged with the British Lung Foundation) and the Allergy & Asthma Network. The committee planned the forum (including arranging the venue, timing and financing), solicited, selected and organised abstracts for presentation, and performed follow-up activities.

Solicitation and selection of abstracts

Abstracts were solicited from interdisciplinary early-stage career asthma researchers who had published innovative approaches to studying and managing asthma, with a particular focus on non-T2 asthma. Abstracts were evaluated using a standard scoring rubric (supplementary table S1) with specific attention to whether the abstract addressed one of the asthma research priorities identified by the European Asthma Research and Innovation Partnership (supplementary table S2) [17]. An important goal was creating a diverse, multi-national panel of early-stage career investigators. Once the review of the abstracts was complete, they were grouped into categories (table 1).

Forum

There were two parts to the forum. Part 1 was online *via* Zoom, with 5-min presentations by each presenter. During the virtual forum, participants posed questions to the presenter through the chat function.

TABLE 1 Abstract categories

General omics and big data analysis
Lung–brain axis and airway neurology
Sex differences in asthma
Paediatric asthma and the differences between childhood and adult asthma
New therapeutic targets: airway epithelial biology
New therapeutic targets: airway and circulating immune mediators
Lung anatomy, physiology and imaging

This was an all-day forum that ran across countries and time zones. Part 2 was an in-person meeting held 1 week after Part 1, just prior to the ATS Annual Meeting. Part 2 consisted of a recap of each abstract followed by Q&A, and breakout group discussions for each abstract category to consider potential for research collaboration, innovation and translation, as well as how each participant could apply the principles of ICAN to their individual research. All participants were invited to bring concrete, actionable ideas for discussion at the in-person forum (supplementary table S3). The meeting was held over 2 days to allow time for further engagement.

Results

Outcomes of the meeting

In all, 55 participants attended the ICAN forum. Authors of the 34 accepted abstracts first met together by category, led by the lead author of the highest scoring abstract in that category. Summaries of these discussions are below. Three themes emerged during the forum. First, research groups are looking for larger datasets and cohorts (through collaborations) to validate and further their research, and there is a need to use available data. Second, an important unmet need is translational research that incorporates the *in vitro* research findings into clinical studies. Third, to optimally implement research findings into patient care there is a need to overcome various technical challenges that hamper translation efforts.

General omics and big data analysis

The focus of this category was a proposal to establish an international consortium that the group named INTERLUDE-A (INTERnational LUng Data rEpository – Asthma). The main goal of this consortium is to develop, host and provide a platform of "big data" (sequencing datasets, imaging and associated metadata) accessible by anyone in the asthma community. The group aims to facilitate data sharing and associated metadata to support asthma research, enable discovery and validate findings from smaller cohorts. Ultimately, the group envisions that INTERLUDE-A will be a worldwide recognised platform in the international asthma community. The meeting at ICAN allowed the creation of the Steering Committee to get the process primed and to enable further, large-scale funding.

The first specific goal is to generate a platform that harbours genome-wide data, imaging and phenotypic data. This platform will not include single-cell RNA sequencing, since there are widely available platforms specialised in this area, particularly the Lung Cell Atlas [18]. The group agreed that this platform should be a federated database where data control remains with the original user; further methods may be implemented in the future. The aim is to generate a user-friendly and up-to-date host for these types of datasets in asthma that are open to collaborators. After attending ICAN it was clear that such a platform is long required and demanded by our community and should include international partners such as those present at ICAN. It was also clear that associated metadata should be coded in a manner that is compatible across datasets to enable adequate and meaningful comparisons matched to patient endotype and phenotype.

There was agreement to develop collaboration to leverage several asthma cohorts such as severe asthma consortium RASP-UK, or the European Union-sponsored severe asthma collaboration Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes (U-BIOPRED). To facilitate these collaborations, approvals by ethics committee will have to be sought and specific requirements by funding agencies will need to be considered.

The group wants to create a live database that is truly sustainable, a platform that can be used for years to come and provides an example for other diseases. It wants to consider the needs of the field, including the generation of a unique code and grammar that we all share and use: a true harmonisation of asthma data. This will enable making new datasets accessible and usable to others, similar to the Lung Cell Atlas [18]. This database will be accessed by people in the field who will need to sign up and be part of the community. The aim is for INTERLUDE-A to be something in which everyone in the asthma field will want to participate.

Since the ICAN meeting, the group has been planning a submission for grant funding, initiated talks with possible platform hosts and explored a potential first meeting of the Steering Committee during the spring of 2023 to continue engagement and planning. Collaborations have been developed with the investigators from the University of Southampton (UK) spin-out company TopMD, to create global, three-dimensional gene expression maps of RNA response patterns to therapies. The initial collaboration will involve the response of the circulating transcriptome to dehydroepiandrosterone (DHEA) treatment (see also section "Sex differences in asthma").

Lung–brain axis and airway neurology

Specific questions for future collaboration and study emerged for this category, focusing on mechanisms, relationships and treatments of psychoneurological factors and asthma (table 2).

Since the ICAN meeting, collaborations among ICAN participants included a successful joint symposium proposal to ATS 2023. The collaborations have resulted in the discovery that the U-BIOPRED dataset has a time stamp, and funding has been obtained to begin work on analysing this dataset for a time-of-day signal. A new collaboration is being discussed for use of human epithelial tissue from severe asthma patients and to develop an air–liquid interface (ALI) bronchial epithelial cell culture model. Culture methods for murine airway epithelium are being developed to investigate how the molecular clock in bronchiolar epithelial cells controls epithelial barrier function by time-of-day. These exciting collaborations will lead to joint transatlantic grant proposals and publications, combining clinical data from severe asthma patients with mechanistic mouse studies, enabling a thorough understanding of epithelial barrier function in asthma.

Another collaboration that started since the ICAN meeting involves the physiological and psychological responses to various treatments in severe and difficult to manage asthma. Neuroimaging investigation is commencing to examine structural brain changes associated with wellbeing improvements in people with severe asthma who are starting biologic therapies. Furthermore, the clinically relevant effects of mindfulness psychological therapies for people with asthma is under investigation and has shown improvements in asthma control, reductions in distress and reductions in exhaled nitric oxide (compared to waitlist controls).

Sex differences in asthma

The focus of this category was to create a global collaboration to investigate further the effect of sex and sex hormones on asthma severity. This group focused on data exchange to help discover the biological mechanisms underlying sexual dimorphism in asthma. Specific questions for future collaboration and study emerged for this category, focusing on sex-specific differences in gene regulation and protein modification (table 3).

Since the ICAN meeting, several collaborations have been explored to study the effect of androgens on asthma immunology. These include a collaboration between US investigators and TopMD in the UK to determine whether there are sex differences in existing data and cohorts and the transcriptomic effects of androgens on patients with asthma, a collaboration between US and U-BIOPRED investigators to replicate the sex-specific data from the Severe Asthma Research Program (SARP). A collaborative clinical trial is

TABLE 2 Questions for future collaboration and study related to the lung–brain axis and airway neurology in asthma

What are the effects of asthma biological therapies on related brain manifestations such as depression, anxiety and cognition?
What is the relationship between dyspnoea and depression in asthma, and how does serotonin play a role?
Should collaborative trials of 5-hydroxytryptamine supplementation in asthma be considered?
Are there meditation techniques that can objectively benefit asthma?
What is the effect of lung denervation following lung transplantation on asthma?
Are there differences in capsaicin sensitivity between men and women?
Is there a role for TSLP in capsaicin sensitivity?
What is the effect of circadian rhythm on disease manifestations (*e.g.* symptoms, spirometry), and how may it impact diagnosing asthma or collecting data?
What is the effect of biological rhythms on responsiveness to asthma treatment?
What are the effects of corticosteroids on epithelial and neuronal clock genes in the airways?

TSLP: thymic stromal lymphopoietin.

TABLE 3 Questions for future collaboration and study related to sex differences in asthma
How are clock genes differentially regulated in males and females?
Are there sex-specific differences in post-transcriptional dysregulation by microRNAs or RNA-binding proteins in asthma?
Can omics technologies be implemented to understand sex differences or how sex hormones regulate metabolites, gene transcription and post-transcriptional changes?

being planned to determine if DHEA supplementation in individuals with low DHEA will improve asthma symptoms and lung function.

Paediatric asthma and the differences between childhood and adult asthma

The focus of this category was on the reasons for differences between childhood and adult asthma. Of particular interest was the translation of prognostic research into clinical practice using a learning health systems framework. The idea was to design and apply data-driven methodology to understand childhood asthma disease development and to inform prevention. Several proposed innovative collaborations were discussed. First, the investigators proposed leveraging electronic medical records to translate existing childhood asthma prediction algorithms as point-of-care decision support tools and to define clinical phenotypes based on existing "real world" clinical data. The idea was the integration of multiple data sets/sources, including electronic medical records, to support translational research and clinical applications, including decision support, prediction, *etc*. Sources of data would also include environmental exposure, behaviour, social determinants of health, "omics" data, *etc*. Second, they proposed the use of $CD4^+$ single-cell transcriptional profiles to identify a novel phenotype of asthma among obese children. Third, they planned to establish international collaborations for validation of the findings presented at the meeting.

New therapeutic targets: airway epithelial biology

The focus of this category was potential asthma therapeutic targets in the airway. Topics discussed included: 1) antigen stasis and nitric oxide oxidation in the context of ciliary dysfunction; 2) house dust mite allergen and T2 cytokine-mediated epithelial barrier dysfunction attenuated by synthetic Rev-Erb ligands; 3) club cell secretory protein 16 (CC16); and 4) IgE/FcaRI cross-linking on airway epithelial cells as the potential molecular targets for asthma treatment. Specific questions for future collaboration and study emerged for this category, focusing on pathogenetic mechanisms that underlie asthma (table 4).

New therapeutic targets: airway and circulating immune mediators

The discussion in this group focused on IL-6 as a circulating immune mediator of interest based on data presented at the meeting. Specific questions for future collaboration and study emerged for this category, focusing on harmonising the available datasets in the USA (SARP) and Europe (U-BIOPRED), especially the gene transcription datasets, to identify the upstream drivers of the IL-6 pathway in severe asthma and

TABLE 4 Questions for future collaboration and study related to new asthma therapeutic targets in the airway
Do PCD genes (like cystic fibrosis genes) contribute to the pathophysiology of asthma, and can this information be determined using existing international genomic databases in which phenotypic data are accessible?
Would an international collaborative study be possible in which patients expressing PCD genes could use airway clearance techniques to lessen asthma symptoms?
Can dust mite allergen and T2 cytokine-mediated epithelial barrier dysfunction be attenuated by synthetic Rev-Erb ligands in human bronchial epithelial cells?
Do Rev-Erb (NR1D1) enhance barrier function in human airway epithelial cultures at ALI?
Are biobanks from U-BIOPRED and SARP adequate to study human barrier function gene expression in asthma?
Is recombinant CC16 potentially useful as a new asthma drug, particularly for patients with CC16 deficiency?
Can possible single-cell sequencing be used to study the role of epithelial high-affinity IgE receptor in regulation of epithelium disruption and sub-epithelial immune response?
Can topical IgE receptor or EGFR blocker be used as a preventive and/or therapeutic drug for severe atopic and non-atopic asthma?

PCD: primary ciliary dyskinesia; ALI: air–liquid interface; U-BIOPRED: Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes; SARP: Severe Asthma Research Program; CC16: club cell secretory protein 16; IgE: immunoglobulin E; EGFR: epidermal growth factor receptor.

TABLE 5 Questions for future collaboration and study related to new asthma therapeutic targets among circulating immune mediators

What is a hypothesis that could be tested in an international collaboration and its ideal framework?
Is there a way to develop common signatures that can track patients noninvasively across clinical studies/trial cohorts?
Can harmonisation of available data in U-BIOPRED and SARP cohorts expose novel mechanisms or identify predictors of clinical response in subgroups of patients with asthma?
Is the IL-6 signature identified in the U-BIOPRED cohort similar to SARP?
Does the timing of data collection for clinical studies have an impact on clinical data collection and outcome measures such as IL-6 and other circulating mediators?
How can timing factors related to the circadian rhythm be identified and managed for accuracy?

U-BIOPRED: Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes; SARP: Severe Asthma Research Program; IL-6: interleukin-6.

to determine the interaction between IL-6 and classical cells and mediators of inflammation in asthma (table 5). The impact of biological sex, obesity and metabolic dysregulation were identified as key variables to consider in the analyses.

Since ICAN, the group has had several meetings and has agreed on the aims and the way forward for cross-validation across the US and European datasets.

Lung anatomy, physiology and imaging

The focus of this category centred on novel techniques including vascular and other forms of imaging and quantitative computed tomography in the study of asthma, as well as important physiological questions. Specific questions for future collaboration and study emerged for this category, focusing on integration of imaging data with disease mechanisms and the impact of obesity on treatment response (table 6).

Since the ICAN meeting, collaborations with other ICAN participants are being explored to collect similar datasets (computed tomography images, demographics and clinical data) from other cohorts in different countries to expand our current research with functional lung computed tomography analysis to multiracial/multicultural data.

Overall ICAN forum follow-up

The guest speakers discussed practical tips on translating innovative research into business opportunities, and the strategies and challenges of healthcare data integration. Specific talks included details on how to start a company, how to identify an ideal startup leadership team, how to identify and to approach investors, and the basics of bioinformatic analysis and integration of large databases.

Results from a post-event survey indicated that nearly all respondents (25 out of 27) strongly agreed that the categories and topics discussed at the forum were relevant to their research (supplementary figure S1). Most respondents (24/27) also indicated that they were either somewhat or extremely likely to use the information or opportunities they found at the forum (supplementary figure S1). In response to open-ended questions, respondents lauded the strengths of the forum and provided suggestions for future forums (supplementary table S4).

TABLE 6 Questions for future collaboration and study related to lung anatomy, physiology and imaging

How can imaging data from multicentre studies be further integrated with biomolecular readouts?
How can such an integration be made more mechanism-oriented rather than associative?
Can access to samples and/or data already collected (from consortium/networks) further translational imaging investigations, and could this same access allow for expansion from single-cohort findings or to ask additional research questions related to specific areas of interest?
Can *a priori* inclusion and stratification of obese and non-obese persons, with and without atopy or asthma, provide additional useful data in future studies?
Do interventions directed at reducing obesity or obesity-related inflammation/metabolic dysregulation improve asthma outcomes and if so, what mechanisms are involved in response *versus* non-response to such interventions?

Follow-up activities

At the conclusion of the in-person forum, each person was challenged to write down one step they would take in response to the forum. The organising committee followed-up with each participant to see if the step had been taken and any results from the step. In response to this challenge, several participants did indeed follow-through with their step and indicated that new collaborations were being formed as a result of their actions. In addition, a representative from each research category was asked to complete discussion prompts in response to the forum that were essentially the same as those completed between Part 1 and Part 2 of the forum (supplementary table S3) and return the responses to the organising committee.

Discussion and conclusions

Innovative new research in asthma is needed to expand beyond the focus on T2 inflammation to meet the considerable burden of asthma that continues to persist, even in the age of biologics. Through ICAN, interdisciplinary research teams have developed innovative research ideas and new collaborations. The results from these collaborations should enrich and speed up the process through which research can be translated into patient care. Leaders of the ICAN groups were, for the most part, early-stage or mid-career investigators who will be leaders in the next generation of asthma investigators; and data were shared by investigators from five continents. The combination of fresh ideas and energetic, collaborative, global participation enabled the ICAN to provide a firm foundation for efficient and effective asthma research in the future.

Several important concepts emerged from this first ICAN meeting, and young investigators brought novel ideas, perspectives, approaches and data to the discussion. First, the need for greater integration of international databases and cohorts was emphasised. This integration is needed to validate observations made in one study/cohort/database using different populations; to compare populations; to increase the power available to test new hypotheses; to provide a framework for new, prospective studies; to integrate informatic and physical biobanks across studies and across nations; to integrate wearable data with other biobanked data on a large scale; and to perform large-scale post-marketing analyses with a view towards optimised personalised approaches to asthma. This integration forms the basis of INTERLUDE-A and will also be carried forward through individual interactions established at the meeting. Second, there was renewed interest in the lung–brain axis, not only in terms of the classical autonomic and nonadrenergic noncholinergic signalling pathways in the lung, but also in terms of the relevance of the interface between pulmonary conditions and psychiatric disorders, as well as the role of neuronal and pulmonary expression of clock genes in the pathophysiology and treatment of asthma. Third, the relatively dramatic increase in our understanding of the role of sex hormones was reviewed, with particular emphasis on evidence that expression of androgen regulatory HSD3B1 (hydroxy-delta-5-steroid dehydrogenase, 3 β- and steroid delta-isomerase 1) and of airway androgen receptors have an important protective effect in asthma. Fourth, there was a focus on understanding asthma across the lifespan, with a particular interest in the reasons behind the “eye of the hurricane”, in which children have a decrease in asthma severity and a switch from male predominance to female predominance is observed in late adolescence and young adulthood. Fifth, novel airway epithelial targets were reviewed in detail, including both barrier function targets like Rev-Erb ligands and epithelial immune targets for therapeutic development. A sixth area of focus was circulating immune cells and mediators that can be targets for asthma therapy, including non-T2 cytokines such as IL-6. Finally, there was an important focus on old-fashioned pulmonary anatomy and physiology, both in the context of novel measurements of asthma severity and in the context of imaging. Excitement surrounding young investigators interested in new approaches to asthma management was clearly evident.

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