Asthma still kills:

Urgent priorities for the international research community to treat, prevent and cure asthma

Contents

Foreword

I am delighted to endorse this timely report by Asthma UK and many of the respiratory experts who attended last year's Academia Europaea meeting in Cardiff. The meeting focused on an exploration of the mechanisms underpinning non-T2 asthma and made it very clear that our understanding is, indeed, incomplete. The Academia Europaea meeting made a compelling case for more research funding into the broad group of different phenotypes collectively classified as non-T2 asthma. A significant number of all people with asthma are included in this group, but conventional treatments, unfortunately, offer little or no benefit to the sufferers. As discussed at the meeting and summarised in the different presentations, there are many expressions of asthma where the patients can only be partly controlled by the addition of high doses of oral steroids, resulting in severe, long-term adverse effects.

The European and international research community now needs to rise to the challenge of undertaking imaginative and collaborative research that will lead to new treatments for people with non-T2 asthma. This large group of patients has been left behind for far too long in the recent quest for new asthma treatments, which have remained focused on T2 asthma phenotypes. There is a great need for the funding of sustainable international consortia where scientists, clinicians and patients can collaborate to develop and undertake new, transforming asthma research. There is also a need for support of focused translational projects which address matters that have been largely neglected, such as, for example, the gender differences that seem to affect both immune-regulation and physiological control, as well as the emerging evidence that neurobiological reactions also contribute to asthma.

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Executive summary

- An estimated 5.4 million people in the UK, 30 million people in Europe and around 330 million people worldwide have asthma.
- The toll that asthma takes on human health globally is significant and a large proportion of people with asthma are still not receiving adequate treatment: they are living with debilitating symptoms that are affecting their quality of life and ability to carry out day-to-day activities.
- There are two main asthma sub-types, T2-high (eosinophilic) and non-T2 (non-eosinophilic) asthma; non-T2 asthma often remains poorly controlled because of the different mechanisms at work in this form of the disease which are not well understood.
- While non-T2 asthma affects up to a half of all asthma sufferers, the conventional drugs used to treat asthma, such as inhaled or oral steroids, are largely ineffective in this group; nonetheless patients with non-T2 asthma are still sometimes prescribed high doses of oral steroids, with devastating clinical side-effects if used in the long term.
- There has been little progress in the conventional treatments used to treat asthma over the past 30 years, except for new biologic drugs which currently benefit only a small number of patients with T2-high asthma.
- This report focuses specifically on six poorly-understood mechanisms at work in non-T2 asthma which warrant further research: sex hormones; the microbiome; the nervous system; air pollution; poor / incomplete response to steroid therapy in severe asthma; and primary prevention in children at high-risk of asthma.
- New research funding is urgently required to support investigations into these complex mechanisms at work in non-T2 asthma, to support the development of innovative, clinically-proven treatments.
- To be successful in benefiting patients, future research needs to be characterised by national and international interdisciplinary collaborations, supporting shared knowledge and data analysis to more rapidly drive our understanding of non-T2 asthma.
- New technologies should be deployed to help develop innovative therapeutic solutions, including more personalised, targeted treatments for people with non-T2 asthma, using biomarkers to determine, with greater accuracy, their triggers and particular asthma phenotype.
- To take forward our knowledge of non-T2 asthma we therefore specifically recommend:
    - Publishing and disseminating a state-of-the-art academic publication on non-T2 asthma.
    - Establishing a joint European Respiratory Society (ERS) / American Thoracic Society (ATS) task force to address the need for research into non-T2 asthma, with the aim of publishing a joint research roadmap.
    - Working with the ERS Research Agency to create innovative multidisciplinary consortia that take advantage of new technologies and new trial designs to advance our understanding of asthma.

- Developing a call topic for the Innovative Medicines Initiative (IMI) that combines existing multi-omic data sets with novel data sets to identify different types of non-T2 asthma and new drug targets.

- Establishing transnational collaborations to ensure that non-T2 asthma research progresses at pace and scale through the pooling of knowledge and infrastructure.

- Applying artificial intelligence to analyse complex data sets to allow learning from other disease areas that is applicable to non-T2 asthma.

There can be no further delay in developing new therapeutic targets for people with non-T2 asthma who currently have few safe and effective treatments.

A call to action for national and international research funding into non-T2 asthma

Attendees at the joint Asthma UK / Academia Europaea meeting in November 2018 are calling on the European Union and other funders of medical and scientific research to allocate new funding to investigate poorly-understood mechanisms in non-T2 asthma, leading to the development of new treatments for the millions of people who have poorly-controlled asthma – and, eventually, to a cure.

1. Asthma: how we currently treat one of the most common and debilitating long-term health conditions

Asthma is one of the most common and debilitating long-term health conditions, affecting people of all ages, from children to the elderly. An estimated 5.4 million people in the UK[1], 30 million people in Europe under 45[2] and around 330 million people worldwide[3] have asthma. Figures for the annual number of deaths globally due to asthma vary from around 380,000[4] to 420,000[5] and in the UK alone, around three people die each day as a result of having an asthma attack[6]. The toll that asthma takes on human health is therefore significant, and a large proportion of people with asthma globally are still not receiving adequate treatment. The annual economic burden of asthma in the 28 EU countries was estimated at €19.5 billion in conventional direct costs (healthcare) and €14.4 billion in indirect (lost production) costs in 2011[7], although updated data on this would be welcome.

The mainstay of treatment for most people with asthma is regular inhaled low- to medium-dose corticosteroids (ICS) and inhaled salbutamol as needed, with high-dose ICS and long-acting bronchodilators and oral corticosteroids (OCS) reserved for those with uncontrolled symptoms (estimated to be between 5-10% of the asthma population)[8]. OCS cause short- and medium-term side effects such as sleeplessness and weight gain, and in the long-term can lead to a wide range of conditions such as diabetes, hypertension, cataracts, osteoporosis, glaucoma, skin disease, reflux oesophagitis, non-alcoholic fatty liver disease and obesity[9].

Treating asthma of all types is clearly placing a significant burden on healthcare systems across the world. Many people with asthma, especially severe asthma, struggle to live a normal life because of the debilitating symptoms they experience, placing significant limitations on their ability to work, live a fulfilling life and contribute to society. This needs to change

It's not 'just asthma'

- It is estimated that around 400,000 people around the world die prematurely from asthma each year[10].
- Around 50% of those who die from an asthma attack are only being treated for a mild to moderate form of the disease[11].
- At least 60% of asthma deaths are avoidable[12].
- The total annual cost of asthma in the EU amounts to around €35 billion: €20 billion in healthcare costs and €15 billion in lost economic production[13].
- A high number of school days are missed, and workdays lost, in children and adults with asthma[14].
- In 2017, asthma was listed as the 16th highest worldwide cause of YLD (years of healthy life lost as a result of an injury or disease), ranking higher than epilepsy and ischaemic heart disease[15].

A brief history of asthma treatments

Asthma was originally thought to be a disease of airways smooth muscle, a concept which drove the development of bronchodilator drugs. The first asthma guidelines written in 1989[16] highlighted the role of airways inflammation and controller (anti-inflammatory) therapies (inhaled cromones / corticosteroids) were subsequently developed, with some success, although it is clear they are not the 'golden bullet' that many thought they would be. Despite extensive research effort, there has been limited success for asthma drug discovery pipelines since this time. The majority of patients are still being offered the same basic reliever (usually blue) and preventer (usually brown) inhalers as the mainstay of their treatment that they were 30 years ago. The pharmaceutical industry has been reluctant to invest in new asthma treatments despite the medical need. This is because of the high attrition rate in the development of novel asthma therapeutics due to a combination of substantial research and development costs, a lack of suitable models that truly mimic the disease in humans and our poor understanding of the underlying mechanisms underpinning the disease.

> "Despite extensive research effort, there has been limited success for asthma drug discovery pipelines since the late 1980s and the majority of patients are still being offered the same basic reliever and preventer inhalers as the mainstay of their treatment that they were 30 years ago."

The discovery in the 1990s that various cytokine and chemokine networks were associated with the development of asthma stimulated the development of biologic therapeutics to target numerous asthma pathways. The ambition was to modulate the immune system to 'cure' asthma, rather than just to treat the symptoms. Several biologic therapies were developed which are now starting to be used in the clinic. What is becoming clear, however, is that efficacy depends on careful patient selection based on specific biomarkers; for example, biologics targeted against the cytokine IL-5 work best in those with severe asthma in combination with raised blood eosinophil levels. It is also now clear that 'asthma' is only an umbrella term for many different types of wheezing illnesses.

What can we learn from previous asthma research?

Example 1: anti-IgE treatment

Omalizumab is currently the only available therapy targeting the main antibody (IgE) involved in some types of asthma. Omalizumab is approved for use in patients with severe allergic asthma and high IgE blood levels. Initial clinical studies evaluating the efficacy of omalizumab in asthma showed that this anti-IgE monoclonal antibody significantly inhibits early- and late-phase asthmatic reactions triggered by inhaled allergens. Subsequently, a series of randomised controlled trials have shown that add-on treatment with omalizumab is effective in reducing respiratory symptoms, especially asthma exacerbations, hospitalisations, emergency room visits and use of oral corticosteroids in patients with moderate-to-severe asthma[17].

A key factor, however, in the success of anti-IgE therapy is appropriate patient selection, with the best therapeutic results likely to be achieved by treating severe, inadequately controlled and oral steroid-dependent asthmatics who are experiencing frequent disease exacerbations. A post-hoc analysis of the EXTRA study (A Study of Omalizumab (Xolair) in Subjects With Moderate to Severe Persistent Asthma) has demonstrated that high baseline values of peripheral blood eosinophils and fractional exhaled nitric oxide are helpful in predicting a positive therapeutic response to omalizumab in terms of decreasing asthma exacerbations[18]. However, strongly predictive biomarkers have yet to be discovered.

Example 2: anti-IL5 treatment

Mepolizumab, a monoclonal antibody which binds to circulating IL-5 was found to be safe and effective at blocking IL-5 and reducing eosinophilic airway inflammation when tested using *in vitro* systems and *in vivo* models[19]. Studies in patients with mild to moderate asthma have, however, found mepolizumab to be ineffective in improving end-point clinical symptoms[20]. This raised concerns over the efficacy of IL-5 as a therapeutic intervention in asthma. However, by selecting patients with severe disease and a high exacerbation rate, as well as evidence of raised levels of blood and sputum eosinophils, and by choosing an endpoint (number of asthma attacks) more closely associated with the severity of eosinophilic asthma than lung function, subsequent studies[21] with mepolizumab have shown significant reductions in asthma exacerbation rates.

2. What about the people who respond poorly to conventional treatments?

It is becoming clear that what we describe as 'asthma' is not a single disease, but rather a heterogeneous disease with two broad subtypes: T2-high asthma (also termed eosinophilic asthma) and non-T2 asthma (also known as non-eosinophilic asthma). Whilst the mechanisms in T2-high asthma have been reasonably (but not completely) well defined as involving type 2 cytokines, IL-4, IL-5 and IL-13, those driving non-T2 asthma have not. In fact, the best definition we currently have is 'not T2-high'. Non-T2 asthma is, broadly, more common in patients with adult onset asthma, in particular women and in asthma driven by obesity, air pollution, smoking and viral or bacterial infections[22]. It is also clear that within these two broad groups there is further heterogeneity with multiple endotypes. For example, not all patients with eosinophilic asthma respond in the same way to biologics targeting T2 cytokines, with some being 'super-responders' and others having a substantially lesser response, despite their asthma appearing similar in terms of clinical characteristics[23].

While these two broad asthma subtypes may have different triggers and mechanisms, patients still generally present with the same characteristic asthma symptoms: breathing difficulties, chest tightness, coughing and sudden, sometimes catastrophic worsening of symptoms, called asthma attacks.

Figure 1: *The two main asthma sub-types*

T2-high or eosinophilic asthma	Non-T2 or non-eosinophilic asthma
This type of asthma is driven by inflammation of the airways linked to white blood cells known as eosinophils.	This type of asthma is driven by other, sometimes poorly understood mechanisms, and is characterised in some cases by neutrophilic (rather than eosinophilic) airway inflammation, or paucigranulocytic airway inflammation (normal levels of both eosinophils and neutrophils), possibly triggered by environmental exposure to bacterial endotoxins, including air pollution and ozone, as well as viral infections and potentially hormones.
Affects ~37-50%[24] of the asthma population	Affects ~50-63%[25] of the asthma population

Whilst it is encouraging that we now have treatments that are effective in a substantial proportion of people with eosinophilic asthma and we are getting more insights into non-T2 asthma[26], the lack of an in-depth understanding of non-T2 asthma is problematic because it has become evident that it responds only poorly to the long-standing, conventional treatments traditionally used to reduce inflammation of the airways such as ICS. There are many different triggers and mechanisms at work in non-T2 asthma which have not yet been adequately investigated and which are, therefore, only poorly understood. This means that for those people who do not respond well to ICS and who are not suitable for the new biologic drugs, there are no effective alternatives to high dose OCS. In fact, treatment with high-dose OCS in steroid-refractory asthma is futile and it skews the risk:benefit ratio more towards the risk. In the 21st century, people in their 20s and 30s still have to endure a lifetime of treatment with toxic drugs that are very likely to result in significant morbidity and increased mortality in later life. This is simply not acceptable.

"The effects of corticosteroids have taken me from a fit active person to someone with severe osteoporosis and cataracts that substantially limit my ability and vision."

Asthma UK patient representative

3. Setting a joint R&D agenda for asthma amongst patients, researchers and pharmaceutical companies to drive innovation and improve outcomes

In 2013, the European Asthma Research and Innovation Partnership (EARIP), comprising members from two pan-European patient organisations, seven academic institutions and two pharmaceutical companies, initiated and coordinated by Asthma UK, set out to develop a comprehensive approach to asthma research and to set developmental priorities linking basic, translational and clinical science, health service innovation and drug development. This is the first time that policymakers, researchers, clinicians, the pharmaceutical industry, healthcare technology companies and people with asthma came together to harmonise their numerous individual efforts, to enable focus and prioritisation on significantly reducing mortality and morbidity from asthma.

In 2017, EARIP partners published a number of papers[27, 28, 29], including a roadmap[30] setting out where the research and investment focus should be over the coming decade. The work done through this coalition highlights the critical gaps in our basic understanding of asthma and shows how we can drive innovation and competitiveness in order to prevent, manage and, eventually, cure asthma.

The top priority for all the EARIP stakeholders was 'to identify, understand and better classify the different forms of asthma, their progression, and their effects on airway inflammation and the immune system'. The further unpicking of the mechanisms underpinning different asthma phenotypes and the identification and development of new therapeutic targets is now vital for reducing asthma morbidity and mortality across the globe.

4. Where to now? New therapeutic targets for non-T2 asthma

In the absence of any clear direction for the development of new treatments for non-T2 asthma, in late 2018, Asthma UK and Academia Europaea convened a group of global asthma experts – including academics, people with asthma and representatives from major pharmaceutical companies – to discuss 'where to next' for curing and preventing asthma. The group agreed unanimously that there remains a substantial unmet need for effective therapies for people with non-T2 asthma.

Global leaders in their field presented state-of-the-art data on the role of biologics in treating eosinophilic asthma, illustrating how far we have come in developing effective treatments for this asthma subtype, although as mentioned above, it is also clear that even the underlying mechanisms of T2 asthma remain incompletely understood. This was followed by presentations and discussions on some of the potential mechanisms underlying non-T2 asthma: the role of sex hormones; the lung and gut microbiome; neural pathways and air pollution.

There was broad agreement that there needs to be a concerted effort by the international asthma research community, funders and the pharmaceutical companies, to develop new therapeutic targets for non-T2 asthma. New technologies such as multi-omics profiling and artificial intelligence – and new approaches such as real-world trials – could vastly accelerate our understanding. This research could lead to novel, targeted interventions that treat (or prevent) the mechanisms underpinning non-T2 asthma.

5. The next five years: building our understanding of the mechanisms underpinning non-T2 asthma

i. Poor / incomplete response to steroid therapy in severe asthma

Severe / refractory asthma is classified as poorly-controlled disease despite recommended therapy. Steroid-resistant asthma is a subset of severe asthma characterised by poor or no response to steroids. Approximately 5-10% of adult patients with asthma meet the criteria for steroid-resistant / refractory asthma and this subset consumes a disproportionate amount of the healthcare budget in Europe due to increased utilisation of healthcare resources, including outpatient clinic visits, emergency room care and hospitalisation due to asthma exacerbations and asthma attacks. They are also prescribed high doses of medication with little or no clinical effectiveness for their form of the condition.

There is a substantial unmet healthcare need for people with steroid-resistant / refractory asthma.

Severe asthma is a heterogeneous, multi-dimensional disease involving many different confounding factors. It is, therefore, unsurprising that steroid therapy is not successful in all patients. These patients may be unresponsive for several reasons:

- Non-adherence
- Steroid resistance
- Steroid non-response – asthma driven by non-T2 mechanisms

What could drive forward research in this area?

- New technologies to increase adherence to steroid therapy (smart inhalers / connected inhalers).
- Biomarkers: non-invasive, easy to collect biomarkers are urgently needed to identify different subsets of patients who would benefit from different treatments and to use in clinical trials as markers of response to treatment.
- New models to understand poor steroid response.
- Collaborative trial designs with multiple treatments to identify therapies that work in biomarker-defined subgroups of participants with severe asthma.
- Further research into the mechanisms of steroid-unresponsive severe asthma.

Case study: Long-term use of oral steroids

Mel, aged 27 and living in the UK, has struggled with allergies her whole life, but it wasn't until she was about 15-years-old that she started experiencing problems with her breathing. At first, she thought this was just another allergy symptom, so she put up with it until she was struggling so much that she was forced to book an appointment with her GP.

Mel's GP immediately diagnosed her with asthma and gave her a preventer inhaler and a reliever inhaler. These helped Mel with her symptoms quite quickly, however she didn't realise that she was meant to continue taking her preventer inhaler even when she felt well. A few years later, Mel ended up at her GP surgery again with breathing problems and the receptionists recognised that it was so severe that they needed to call an ambulance. She was admitted to hospital and diagnosed with severe asthma and a chest infection, which is what had triggered her asthma attack.

Since this first chest infection four years ago, Mel has been admitted to hospital countless times, often going in for two to six weeks at a time, followed by two to four weeks at home before being admitted to hospital again. She says that 80% of the time she is admitted because her asthma is triggered by another chest infection.

Mel has been taking steroid tablets every day for four years now; she says that she hates taking them but doesn't have any other choice. She has tried to reduce her dose in the past, but this only leads to another hospital admission. High strength steroid tablets taken over a long period of time can have serious and debilitating side effects and Mel says she has experienced many of them.

These side effects have had a huge impact on her daily life. She has doubled in weight from around 50 to 100kg and has been experiencing severe problems with her muscles and bones. The combination of extended periods of time in a bed in hospital and the side effects of the tablets means Mel has lost a large amount of muscle mass. This has left her barely able to walk and she has to use crutches to get anywhere. Despite working hard at physiotherapy, her physiotherapist says it won't be long before she is in a wheelchair which Mel is devastated about. She says she is fighting a losing battle but still has to try.

Mel also has osteoporosis – or thin bones – from taking the steroid tablets for so long. This, combined with her loss of muscle mass, has left her spine unsupported and crumbling. She says that her spine is slowly collapsing and that she is in immense pain every day. She has to take a cocktail of painkillers just to manage her pain. Because her bones are so fragile, Mel has previously broken her sternum and ribs from coughing. Her nurses have banned her from watching comedy programmes on television after she ended up in intensive care from laughing when she had a broken rib.

Mel also experiences problems with her eyes and her skin because of the oral steroids and she spent a six-month period covered in bandages and dressings because her skin was so thin that it would tear at the slightest knock. She has also been diagnosed with cataracts which has left her unable to drive because her vision is so obscured.

Mel has found the cataracts one of the hardest things to deal with as she feels as though she has completely lost her independence with not being able to drive. She says it is difficult for her to use public transport as it is infrequent in her area and there is not always a seat at the bus stop if she has to wait.

> "Mel says she feels as though she is trapped in the body of an old woman"

She has had to give up her job as a carer because the side effects of her medication have had such a massive impact on her life and ability to get around. Mel also explains how difficult it is to be admitted to hospital so frequently. She says she has missed countless birthdays and Christmases because she has been in hospital and now doesn't make any plans if it's more than a week in advance because she doesn't know if she'll be able to make it.

Mel says she feels as though she is trapped in the body of an old woman, but knows that breathing is the most important thing and that she needs the steroid tablets to stay alive. She has just started having Xolair injections, (one of the new biologic drugs) which will hopefully help to reduce the amount of asthma flare-ups she has. This should mean she can begin to reduce the dose of steroid tablets she takes and maybe one day stop taking them every day.

ii. The role of sex hormones in the development of asthma

Clinical and epidemiologic studies in children and adults suggest that sex hormones play an important role in the pathogenesis of asthma. Before pre-pubertal years, three out of five people with asthma are boys. After puberty, there is equivalence in asthma prevalence between males and female in adolescence and early adulthood, followed by a higher female prevalence after the age of 40[31]. Fluctuations in hormones during menstruation, pregnancy and menopause are all associated with changes in asthma symptoms[32]. There is also a fall in the incidence of asthma observed in and around puberty in males, which suggests a possible protective effect of male sex hormones. Results from animal studies support these findings: male mice develop less severe allergic asthma than female mice. Sex hormones may therefore contribute to the onset, progression and / or exacerbation of asthma; understanding how they are able to regulate asthma may lead to the identification of new pathways which can be targeted by therapeutic drugs.

The mechanisms by which oestrogen and / or androgen signalling regulate airway inflammation, mucus production and / or airway hyper-reactivity are not fully known. Recent studies suggest that androgens may influence the development of cells called group 2 innate lymphoid cells (ILC2) in males. These are a recently-identified group of cells with the potent capability to produce T2-type cytokines (such as IL-5 and IL-13) which play an important role in the development of allergic diseases and asthma. Sex differences exist in ILC2 number and phenotype in mice, and human asthma and androgens have been found to limit the number of ILC2 precursors in bone marrow, their development *in vitro* and the number of mature ILC2 cells in target tissues. However, additional studies are needed to discover the mechanisms by which androgens exert their effect on ILC2. Regulation of pulmonary ILC2 is therefore a critical area of investigation which could lead to new therapeutics with the ability to inhibit allergic lung inflammation.

What could drive forward research in this area?

- Human studies investigating the effect of androgen receptor signalling on ILC2.
- Research into the mechanisms of androgen receptor signalling on ILC2.
- Use of animal models of asthma to investigate the role of androgen and oestrogen receptor signalling on key immune cell subsets.
- Exploration of the therapeutic potential of selective androgen receptor modulators (SARM) in experimental models of asthma.
- Clinical trials for SARM in the treatment of allergic asthma.

iii. The microbiome and asthma

The microbiome of lungs may contain viruses, bacteria and fungi. Normal lungs have a 'characteristic' microbiome that is altered in a diseased state and several epidemiological studies have indicated the importance of the microbiome in the development and prevention of asthma. A rich microbial environment in early life provides some protection from asthma; conversely the presence of certain pathogens in throat swabs predicts the later development of asthma and is associated with exacerbations of asthma. Differences in the airway microbiota could be important in determining both the pathophysiology and treatment of asthma and further human microbiome studies will be critical to understanding the respiratory microbiota in patients with asthma[33].

The role of the gut microbiome in asthma is also underexplored due to the problems of confounding by antibiotics usage. Consequently, the role, if any, that the gut microbiome has to play in asthma and in asthma heterogeneity is not fully elucidated. The maternal gut microbiome during pregnancy may also influence the development and maturation of the fetal / infant immune system, the infant microbiome and the risk of allergic disease. A limited number of studies[34, 35] have observed some relationships between intestinal bacterial composition and characteristics of asthma, including lung function and the degree of of aero-allergen sensitisation. Further, larger, appropriately powered studies, carefully controlled in relation to antibiotic usage, are now needed. Once important features of the asthma microbiome have been identified, it may then be possible to devise personalised therapeutic strategies for individual patients to include targeted antibiotics, bacterio-therapy to populate the lung with 'good bacteria' and / or vaccination.

What could drive forward research in this area?

- Carefully controlled human microbiome studies, especially during pregnancy with follow-up of infants.
- Multi-centre, non-macrolide antibiotic trials.
- Studies of bacterio-therapy / probiotics for asthma.
- Prevention studies in infants.
- Novel vaccination strategies for asthma.

iv. The impact of the nervous system on asthma – neuro-immunology

A poorly understood feature common to all types of asthma is the presence of dysregulated sensory responses and resultant pathologic reflexes. In patients with asthma, airway irritation, bronchoconstriction and cough are frequently cited as some of the most debilitating aspects of the disease, but these symptoms are often only poorly explained by objective disease markers. Recent studies[36] have revealed novel, neuro-immunologic pathways that regulate both inflammation and sensory responses in the central nervous system (brain, spinal cord) and peripheral nerves. This is a very new area of research which has been driven by cross-speciality collaborations of neuroscientists

and immunologists. Dysfunctional neuronal pathways may be important in the development of asthma and in the genesis of symptom discordance and these pathways may provide new opportunities for therapeutic intervention. This is an exciting new area of asthma research that warrants further exploration.

What could drive forward research in this area?

- Neuro-immunologic research to investigate the pathways in the central and peripheral nervous systems that lead to dysregulated sensory perception in patients with asthma.
- Further research into potential treatments for non-T2 disease targeting refractory symptoms of cough / breathlessness / inducible laryngeal obstruction.
- Clinical trials for compounds and non-pharmacological therapies targeting the neuro-immunologic pathways in asthma.
- Cross-speciality collaborations between neuroscientists, immunologists, the pharmaceutical industry, psychologists and pain researchers.

v. Molecular mechanisms linking air pollution and asthma

In Europe, 90% of city dwellers are exposed to harmful air pollutants. Poor air quality is associated with many premature deaths every year (estimated to be between 28,000 and 36,000 in the UK alone)[37]. Across Europe the figure is much higher: the European Environment Agency estimates that around 400,000 people in Europe die prematurely due to air pollution[38]. A very recent study put this estimate even higher[39]. Short-term exposure to pollution is associated with a reduction in lung function, and during major air pollution episodes many additional patients with asthma are admitted to hospital with breathing difficulties. The role of long-term air pollution in the development of asthma is currently less well researched and should be a major area of research investment. Air pollution may, for example, act by increasing oxidative stress. It could, therefore, be possible to elevate levels of antioxidant defence in patients with asthma to provide protection of the airways from pollutants.

In the United Kingdom, in May 2019, a new inquest was announced into the death of Ella Kissi-Debrah, a nine-year-old girl whose many asthma attacks have been linked to high levels of air pollution near her home. Ella, who tragically died in 2013, lived just 25 metres from the South Circular Road in south east London, one of the capital's busiest roads. A report into her death in 2018 concluded that it was likely that unlawful levels of air pollution contributed to her fatal asthma attack[40].

What could drive forward research in this area?

- Determining the mechanisms by which different components of vehicle exhaust exacerbate and instigate asthma – including nitrogen dioxide (NO_2) and particulate matter from diesel vehicles – as well as investigating the impact of other potential atmospheric triggers such as ozone.
- Studies investigating levels of antioxidant defence in patients with asthma and methods of increasing antioxidants.

vi. Conducting primary prevention trials in children at high risk of asthma

The range of new biologics for adults with asthma has steadily increased. The pharmaceutical industry and associated government agencies have, however, expressed little interest in extending these treatments to children. As it is difficult to conduct trials and studies involving children, the scarcity of relevant paediatric safety data hinders the possibilities for primary prevention trials in high-risk children under five years old[41]. If we want to prevent asthma rather than just treat the symptoms, these studies are essential.

What could drive forward research in this area?

- Creating models for valuation of pharmaceutical research that do not undervalue prevention as part of the treatment armoury.
- Understanding the difference between wheeze and asthma, particularly in pre-school children.
- A new paradigm for acknowledging that children have different mechanisms involved and some treatments may only be effective in children. Safety studies may have to be conducted in adults, but efficacy should by necessity be in children.
- Determining the mechanisms by which asthma switches off in certain children, driving them into remission and trying to replicate this in children not going into remission.
- Creating algorithms that potentially use artificial intelligence (AI) to predict those children with the greatest risk of developing asthma. These are the children in whom we should start to utilise both remissive and preventative treatments. Additionally, it would be valuable to test the risk indices already developed in the different cohorts to see which ones validate and have the most power.
- Standardising the information collected in different studies so risk indices can be studied effectively and honed to perfection.
- Setting up a joint group within the American Thoracic Society and the European Respiratory Society to consider the definitions of prevention, cure and remission and to work with regulators on valid endpoints for clinical studies.

6. The next ten years: time for a new approach

We need to think creatively, ambitiously and strategically about how we drive the development of new therapeutic targets for the many millions of people with asthma who do not respond to currently available treatments, or who have had to rely on oral corticosteroids for decades, often with catastrophic side effects.

Our new research focus should have the following key elements:

i. An emphasis on developing more personalised treatments for asthma patients

Asthma remains sub-optimally controlled in many patients when treated according to the one-size-fits-all approach advocated by existing treatment guidelines. Micro-array studies (which study the extent to which certain genes are turned on or off in cells and tissues) should be used to profile individuals at risk of steroid-resistant asthma. The Refractory Asthma Stratification Programme (RASP-UK) is exploring non-steroid responsive disease as outlined above and, more specifically, non-T2 mechanisms, including exacerbation events that occur whilst on biologic therapy[42]. In the future it will, hopefully, be possible to phenotype and genotype individual patients to determine the best course of treatment. The definition of different asthma phenotypes or endotypes will be an important step towards the use of precision medicine in asthma. Although T2-high asthma is reasonably well-defined, with targets becoming available for treatment, the definition of non-T2 phenotypes is a priority. Personalised healthcare is also dependent on the discovery of biomarkers that can help differentiate between phenotypes and identify patients suitable for specific, targeted therapies.

Another important issue is the consideration of gender in the design and analysis of preclinical studies. So far, medical research and clinical trials have been mainly focused on males, probably as a consequence of the 1977 US FDA guidelines advising that women of childbearing potential should be excluded from drug trials. Emerging evidence shows, however, that gender clearly influences innate and adaptive immune responses in the context of allergic asthma. Gender should, therefore, be taken into consideration to define targets for more effective prevention and treatment of asthma. In the era of precision medicine, to achieve effective treatment for all individuals, men and women will have to be treated differently so that they are protected equally. Gender should be considered a key variable in the development of personalised medicine.

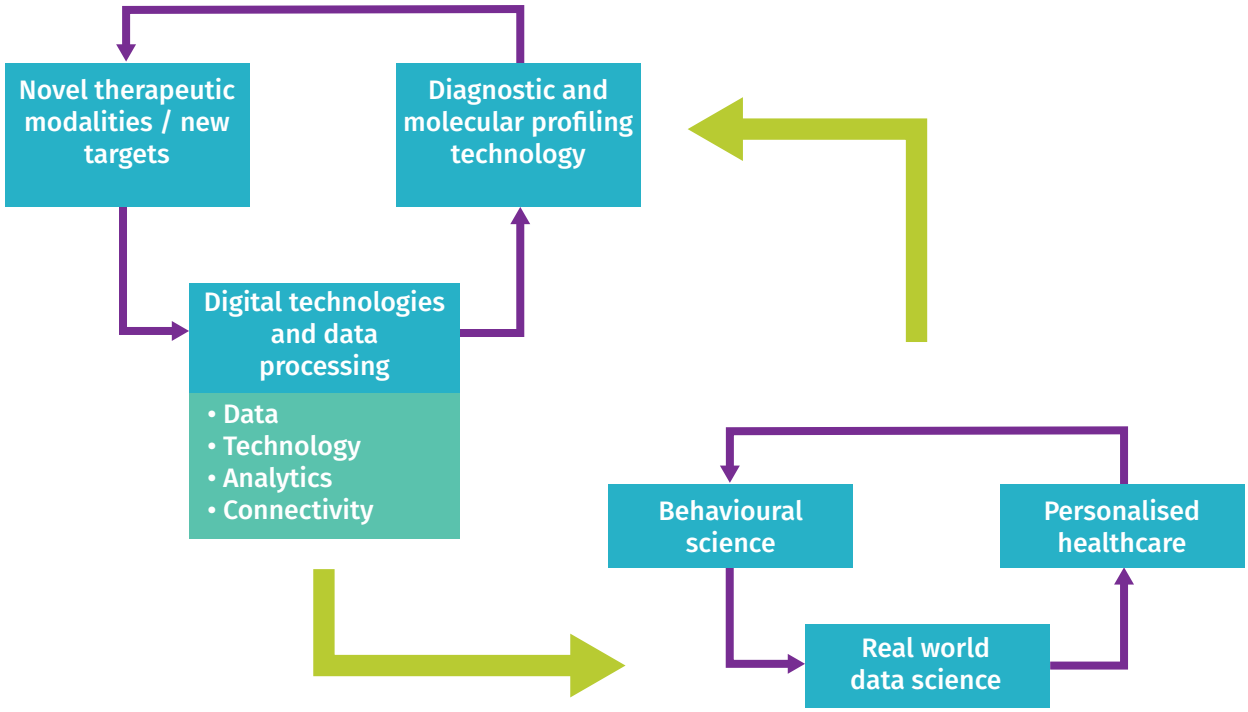
> "There is a significant extra burden on both patients and the NHS of steroid-induced side effects, but as people with severe asthma we accept them to breathe so resign ourselves to the other bits. I have total adrenal suppression now, but at least I'm still breathing!"
>
> **Asthma UK patient representative**

ii. Using new technologies to find new solutions

We are currently living in an era of transformative technological convergence, whereby an array of new technologies, if combined, could drive exponential gains in scientific understanding. To advance our limited understanding of key mechanisms in non-T2 asthma, as outlined in this paper, demands taking advantage of these new technologies to stratify the different types of asthma[43] and identify new targets for treatment.

As we have discussed, asthma is a complex condition that is caused by a combination of genetic and environmental factors and it is recognised that non-T2 asthma is, itself, heterogeneous. It is also possible that the type of asthma someone has changes over time; that is, symptoms are the result of different molecular processes at different times in a person's life[44]. Emerging technologies are enabling us to understand, in unprecedented detail, the molecular interactions in the human body, while new approaches to trial design and the use of digital technologies stand to transform the speed at which targeted treatments can be developed.

Figure 2: *Interdependent evolution of technology and science: faster pace of progress and greater interdependency*[45]



The changes that occur in the underlying pathophysiological mechanisms that result in asthma attacks can greatly benefit from the '-omics' technologies, with the IMI-funded U-BIOPRED research programme[46, 47], being a flagship for how a multi-omic approach can lead to significant gains in our understanding of asthma. Proteomics[48], metabolomics[49], lipidomics[50] and transcriptomics[51] and breathomics have each shown value in identifying some of the different types of asthma[52]. Each of these -omics technologies are expected to drive billion-euro markets in years to come, with the global proteomics market alone expected to be valued at $38.7bn by 2024[53].

As well as understanding the mechanisms that drive non-T2 asthma in greater detail, the heterogeneity of non-T2 asthma should be reflected in trials which include subjects who are more representative of the patients seen in clinical practice[54]. The use of innovative, pragmatic trial platforms that better reflect real-life clinical practice, therefore, has particular relevance to non-T2 asthma[55, 56]. Additionally, digital technologies such as smart inhalers could enable personal monitoring therapy as well as patient-entered data that could be combined with -omics data, and possibly behavioural data, to provide greater insights into the impact of interventions.

To combine and analyse these vast, complex datasets – covering chemical -omics data and clinical monitoring data – technologies such as artificial intelligence (AI) and machine learning will need to be leveraged. Computational approaches such as AI can accelerate the acquisition of drug-target data and promote novel predictions of drugs targets, particularly in the development of combination therapeutics for complex diseases[57]. AI has been used, for example, to discover non-obvious, clinically relevant relationships between asthma medication and renal failure[58].

Machine learning raises the prospect of interrogating large datasets in a free, non-hypothesis-driven manner and it could therefore be useful in the formulation of new hypotheses[59]. There have been some promising applications of machine learning technology to date, specifically latent class analysis which has contributed to distinguishing between asthma and wheezing subtypes in childhood[60]. It is possible that AI and machine learning could reveal significant mechanistic overlap between asthma and other conditions and / or identify targets that can be addressed by existing drugs. However, these technologies remain under-utilised for asthma.

A further, distinct advantage of these new technologies is the prospect of increased drug development success rates. For example, the use of an accepted multi-omic profiling approach would enable the right drug to be given to the right patient which would mean significant reductions in study sample sizes. This would lead to smaller phase 3 trials and reduced failure due to the exclusion of non-responders in studies. The application of AI could also reduce the need for costly new cohorts, and instead enable new insights from existing cohorts.

The combination of -omics technologies, pragmatic trials and new digital technologies that can improve trials and data analysis, represents a remarkable opportunity for future asthma research. To take advantage of these new opportunities demands researchers, funders and innovators to commit to collaborating across disciplines and moving on from traditional, siloed research. Linking public and private stakeholders around common goals[61] could lead to a deeply enriched, 21st century asthma research ecosystem that draws on the expertise in these technologies to deliver breakthroughs for people with asthma.

iii. National and international research collaborations

Moving beyond current barriers in asthma research will require innovation in trial design, effective partnerships with patient groups and effective multinational trials consortia. There are current European and transnational opportunities to conduct clinical trials that could facilitate the development of common trial platforms to maximise overall efficiency and move the field of non-T2 asthma research and knowledge forwards.

Future advances are likely to require parallel advances in biomarker identification and defining endotypes and partnerships with patients, the pharmaceutical industry and funders. A recognition of the important clinical need and the commitment of the funding agencies to supporting research in this area, have opened the doors to exciting potential opportunities for European and transnational collaborations on future clinical trials, to optimise the care of non-T2 asthma.

What can bring together researchers, academia and pharmaceutical companies to work together on shared objectives? To quote the European Respiratory Journal on the benefits of collaborative working: "First of all, scientists come together to undertake better science. Several studies have shown that biomedical research that is carried out through international and interdisciplinary collaboration is of significantly higher quality and impact than research performed by a single centre or discipline."[62] The same must surely be true of collaborative, international asthma research. The pooling of scientific expertise, infrastructure and patients quite simply enables larger and more complex studies to be carried out. The U-BIOPRED project on severe asthma applied as many as ten -omics technologies, knowledge management and data analysis tools for which no single company, academic partner or even country had the required expertise.

In a more recent editorial in the American Journal of Respiratory and Care Medicine, the authors similarly concluded:

"How was it that in a climate of industrial and academic competition, partners were willing to work as one, blurring boundaries between the individual pharmaceutical companies and universities? In all cases, the research undertaken was precompetitive and it focused on basic science and the identification of new targets that all partners could build on and exploit individually. The expense of large projects like U-BIOPRED has been so high that it would have been unaffordable for individual members, including large multinational pharmaceutical companies."[63]

A truly collaborative approach is the only way forward to tackle the current urgent and unmet need in asthma research. Recognising this need, EARIP recommended the creation of a research network comprising relevant stakeholder groups and, in 2018, the European Respiratory Society established SHARP (The Severe Heterogeneous Asthma Research collaboration, Patient-centred), supported by five pharmaceutical companies. To date the collaboration has engaged 27 European countries on a programme to: remove the need for OCS; ensure access to a specialist for all people with severe asthma; improve understanding of disease mechanisms; and prevent moderate asthma from progressing to become severe asthma[64].

iv. Studying patients over time to establish the stability of phenotypes

Longitudinal cohort studies are essential to understand the life course and childhood predictors of asthma and the complex interplay between genes and the environment. Specifically, cohort studies should include boys with asthma to follow them through puberty, during which time a large proportion of them will naturally grow out of their asthma symptoms. We may uncover from this natural process of asthma 'cure', new targets to mimic this process in other individuals with asthma. A huge amount of information can be gained from such longitudinal studies and the complexity of harmonising research protocols and databases needs to be addressed with a well-planned agenda of long-term initiatives. The strategies for analysing such 'big data' sets in networked databases, including decentralised meta-analysis and centralised analysis of pooled data sets, need to be carefully planned however, because these challenges are complex and demanding.

7. Summary and recommendations

The past three decades have seen significant improvements in our understanding of the disease mechanisms in T2-high asthma and the development of new treatments (biologics) targeting T2-high asthma. Despite such major strides, around half of all asthma patients continue to experience asthma attacks and sub-optimal control, and there remain major unmet needs in treating patients with non-T2 asthma. Future progress is likely to require parallel advances in biomarker identification and defining asthma sub-types, as well as partnership with patients, the pharmaceutical industry and funders. A recognition of the significant, unmet clinical need in asthma and a commitment by the funding agencies to support research in this area is now needed; this will open the doors to ground-breaking new opportunities for international collaboration on setting up clinical trials aimed at treating, preventing – and ultimately curing – asthma.

These are the key recommendations of this report:

- To publish and disseminate a state-of-the-art academic publication on non-T2 asthma to drive investment in and focus on non-T2 asthma and new multidisciplinary collaborations.
- To establish an ERS / ATS joint task force to address the need for research into non-T2 asthma, with the aim of publishing a joint research roadmap.
- To work with with the ERS Research Agency to create innovative multidisciplinary consortia that take advantage of new technologies and new trial designs to advance our understanding of asthma.
- To develop a call topic for the Innovative Medicines Initiative that combines existing multi-omic data sets with novel data sets to identify different types of non-T2 asthma and new drug targets.
- To establish transnational collaborations to ensure that non-T2 asthma research progresses at pace and scale through the pooling of knowledge and infrastructure.
- To apply artificial intelligence to analyse complex data sets to allow learning from other disease areas that is applicable to non-T2 asthma.

Asthma UK and Academia Europaea hope that the coming decade will see innovative and life-changing breakthroughs in the treatment of non-T2 asthma.

Glossary and abbreviations

ATS American Thoracic Society.

Biologic A biologic drug is a product that is produced from living organisms or contains components of living organisms.

Biomarker A naturally occurring molecule, gene or characteristic by which a particular pathological or physiological process or disease can be identified.

Endotype A subtype of a condition, which is defined by a distinct functional or pathobiological mechanism.

ERS European Respiratory Society.

Eosinophil A normal type of white blood cell that has coarse granules within its cytoplasm. Eosinophils are produced in the bone marrow and migrate to tissues throughout the body. The numbers of eosinophils in the blood often rises when an allergic reaction occurs.

IgE Immunoglobulin E.

IL Interleukin.

ILC2 Group 2 innate lymphoid cells.

In vitro Studies performed with micro-organisms, cells, or biological molecules outside their normal biological context.

In vivo Clinical research carried out on whole, living organisms or cells, usually animals.

Neutrophil A type of immune cell that is one of the first cell types to travel to the site of an infection.

Paucigranulocytic Meaning with few granulocytes.

Phenotype All the observable characteristics of an organism that result from the interaction of its genotype (total genetic inheritance) with the environment.

SARM Selective androgen receptor modulators.

T2-high asthma types of asthma characterised by high (>300cell / l) blood eosinophil levels.

Non-T2 asthma types of asthma that are caused by mechanisms not driven by eosinophils.

U-BIOPRED Unbiased BIOmarkers in the PREDiction of respiratory disease outcomes.

Xolair (omalizumab) A prescription treatment for moderate to severe persistent allergic asthma and chronic idiopathic urticaria (CIU).

YLD Years of healthy life lost as a result of an injury or disease.

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Every ten seconds someone in the UK has a potentially life-threatening asthma attack and three people die every day. Tragically two thirds of these deaths could be prevented, whilst others still suffer with asthma so severe current treatments don't work.

This has to change. That's why Asthma UK exists. We work to stop asthma attacks and, ultimately, cure asthma by funding world leading research and scientists, campaigning for change and supporting people with asthma to reduce their risk of a potentially life-threatening asthma attack.

We fight asthma in three ways:

- We fund world class asthma research.
- We campaign to improve the quality of care received by people with asthma.
- We help hundreds of thousands of people a year with our expert advice and support.

To find out more about Asthma UK's work:

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