Asthma management through the ages

An expert guided timeline of the key milestones in asthma research and management

Also available as a video featuring Professor Ian Pavord and Assistant Professor Simon Couillard discussing the key milestones in asthma research and management

EpiCentral
UNDERSTANDING THE CENTRAL ROLE OF THE EPITHELIUM IN SEVERE ASTHMA AND BEYOND

Navigational features of this document

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Click on the following icons to:


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Asthma management timeline: era overview*

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To dive into the key milestones, click on the various eras:

An early era of asthma diagnosis and management based largely on patient symptoms…

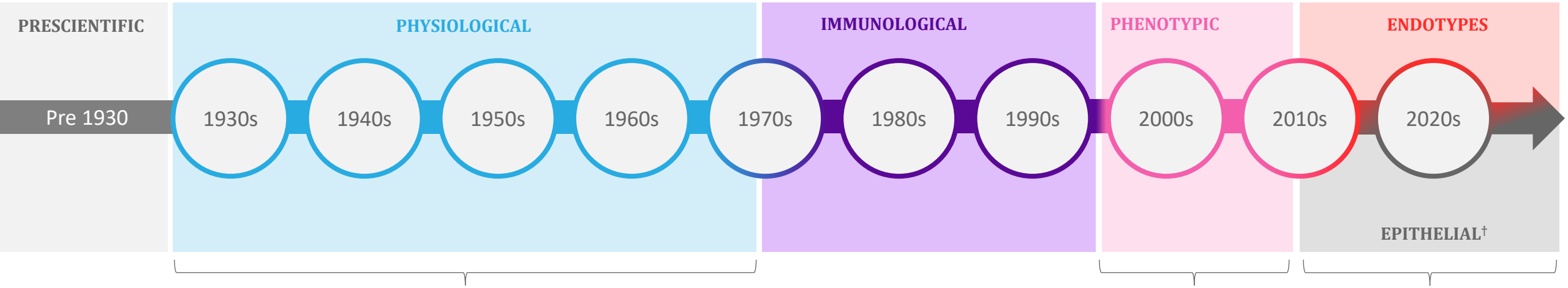
'Prescientific' era

An era of asthma diagnosis and management based on key inflammatory markers…

'Immunological' era

An era of asthma diagnosis and management based on the discovery that specific asthma drivers can be targeted…

'Endotypes' era



'Physiological' era

An era of asthma diagnosis and management based on physiological measures, including spirometry and bronchodilation…

'Phenotypic' era

An era of asthma diagnosis and management based on the discovery that key asthma clusters can be mapped into phenotypes…

'Epithelial' era†

An era of asthma diagnosis using the increasing understanding of the role of the airway epithelium and its potential in mediating asthma…

*Timeframes noted in the era overview are approximate date ranges for each era and further details are subsequently provided.
†The 'Epithelial' era is based on a current theoretical era of ongoing research focused on the epithelium. The views and opinions are those of AstraZeneca and key opinion leaders involved in the creation of this document.

The 'Prescientific' era

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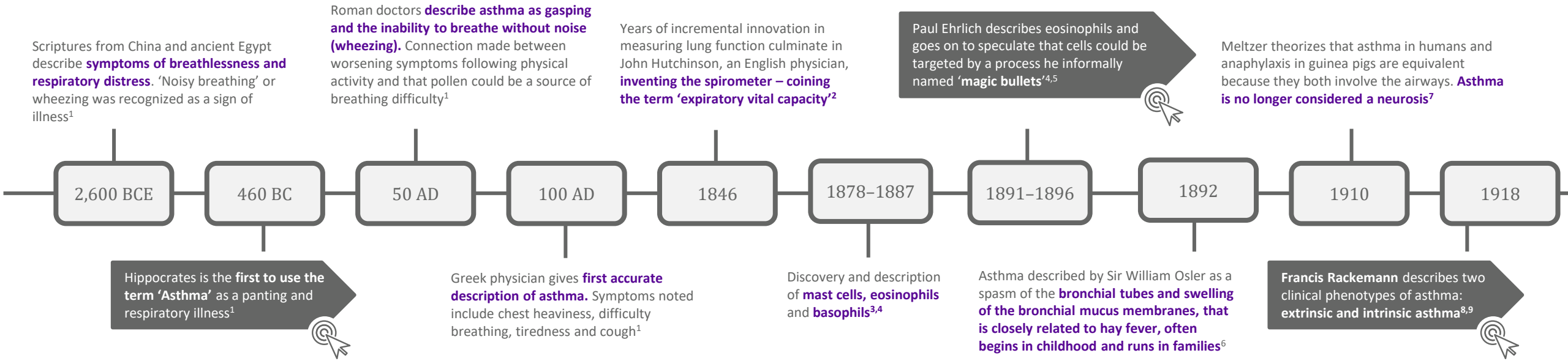
- Traditionally, asthma was classified based on symptoms and clinical characteristics alone. Progress in asthma management was made in the 1800s, where a written definition of asthma was coined by Sir William Osler



Approximate time period: Pre 1930s

References: 1. History of asthma (Part 1): in the beginning. 2017. https://asthma.net/living/history-of-asthma-part-one-in-the-beginning. Accessed October 2023. 2. Kouri A, et al. *Eur Respir Rev*. 2021;30:210081. 3. Diamant Z, et al. *Respir Med*. 2007;101(3):378-388. 4. Valent P, et al. *J Innate Immun*. 2016;8:111-120. 5. Schwartz RS. *N Engl J Med*. 2004;350(11):1079-1080. 6. Holgate ST. *Allergy Asthma Immunol Res*. 2010;2(3):165-171. 7. McFadden Jr ER. *Am J Respir Crit Care Med*. 2004;170:215-221. 8. Rackemann FM. *Arch Intern Med (Chic)*. 1918;12:517-552. 9. Rackemann FM. *Am J Med*. 1947;3(5):601-606.

The ‘Prescientific’ era

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Traditionally, asthma was classified based on symptoms and clinical characteristics alone. Progress in asthma management was made in the 1800s, where

First use of the term ‘Asthma’

The earliest text where the word ***asthma*** is found as a medical term is in the writings of the school of **Hippocrates** of Kos[1]

Asthma derives from the Greek word ‘ασθμα,’ meaning a

‘short-drawn breath, hard breathing, or death rattle’[2]

Want to read more?

References: 1. Marketos SG and Ballas CN. *J Asthma*. 1982;19(4):263-269. 2. Pavord ID, et al. *Lancet*. 2018;391(10118):350-400.

Scriptures from China and ancient Egypt describe **symptoms of breathlessness and respiratory distress**. ‘Noisy breathing’ or wheezing was recognized as a sign of illness[1]

Roman doctors de… **and the inability … (wheezing).** Conn… worsening sympto… activity and that p… beathing difficulty…

Meltzer theorizes that asthma in humans and anaphylaxis in guinea pigs are equivalent because they both involve the airways. **Asthma is no longer considered a neurosis**[7]

2,600 BCE | 460 BC | 50 AD | 1892 | 1910 | 1918

Hippocrates is the **first to use the term ‘Asthma’** as a panting and respiratory illness[1]

…illiam Osler as a …bes and swelling …embranes, that …ever, begins in …amilies[6]

Francis Rackemann describes two clinical phenotypes of asthma: **extrinsic and intrinsic asthma**[8,9]

Approximate time period: Pre 1930s

References: 1. History of asthma (Part 1): in the beginning. 2017. https://asthma.net/living/history-of-asthma-part-one-in-the-beginning. Accessed October 2023. 2. Kouri A, et al. *Eur Respir Rev*. 2021;30:210081. 3. Diamant Z, et al. *Respir Med*. 2007;101(3):378-388. 4. Valent P, et al. *J Innate Immun*. 2016;8:111-120. 5. Schwartz RS. *N Engl J Med*. 2004;350(11):1079-1080. 6. Holgate ST. *Allergy Asthma Immunol Res*. 2010;2(3):165-171. 7. McFadden Jr ER. *Am J Respir Crit Care Med*. 2004;170:215-221. 8. Rackemann FM. *Arch Intern Med (Chic)*. 1918;12:517-552. 9. Rackemann FM. *Am J Med*. 1947;3(5):601-606.

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2,600 BCE

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910

1918

ackemann describes two henotypes of asthma: and intrinsic asthma[8,9]

Approximate time period: Pre 1930s

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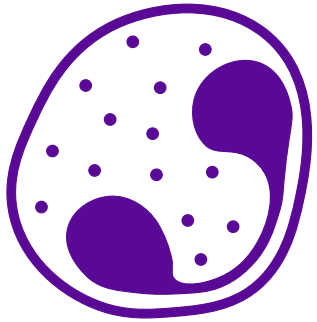
Paul Ehrlich, the eosinophil, and the 'magic bullet'

Ehrlich uses **dye-staining** to **differentiate and describe various leukocytes,** including the eosinophil[1-3]

Ehrlich also develops the concept of a targeted drug informally named a **'magic bullet'** – a drug that would be specific for its target without affecting normal host cells[1-3]



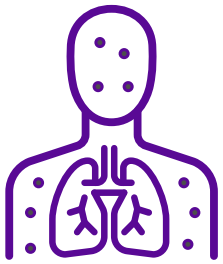
Want to read more?

References: 1. Valent P, et al. *J Innate Immun*. 2016;8:111-120. 2. Schwartz RS. *N Engl J Med*. 2004;350(11):1079-1080. 3. Varricchi G, et al. *Ther Adv Respir Dis*. 2017;11(1):40-45.

Asthma is a complex disease

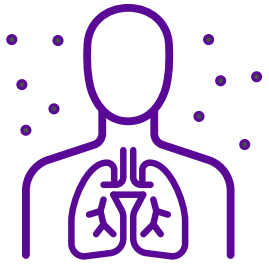
Francis Rackemann highlights the **heterogeneity** of asthma.[1] He distinguishes between **asthma subtypes** based on various observations, including family history, eosinophilia, and treatment[1,2]

Intrinsic asthma



- *Due to factors **intrinsic to the body***
- *Associated with older age at onset*
- *Unlikely to be atopy*

Extrinsic asthma



- *Due to **allergens from outside the body***
- *Associated with younger age of onset*
- *Presence of atopy and other allergic diseases*
- *Environmental triggers*

Want to read more?

References: 1. Rackemann FM. *Arch Intern Med (Chic)*. 1918;12:517-552. 2. Rackemann FM. *Am J Med*. 1947;3(5):601-606.

The ‘Physiological’ era

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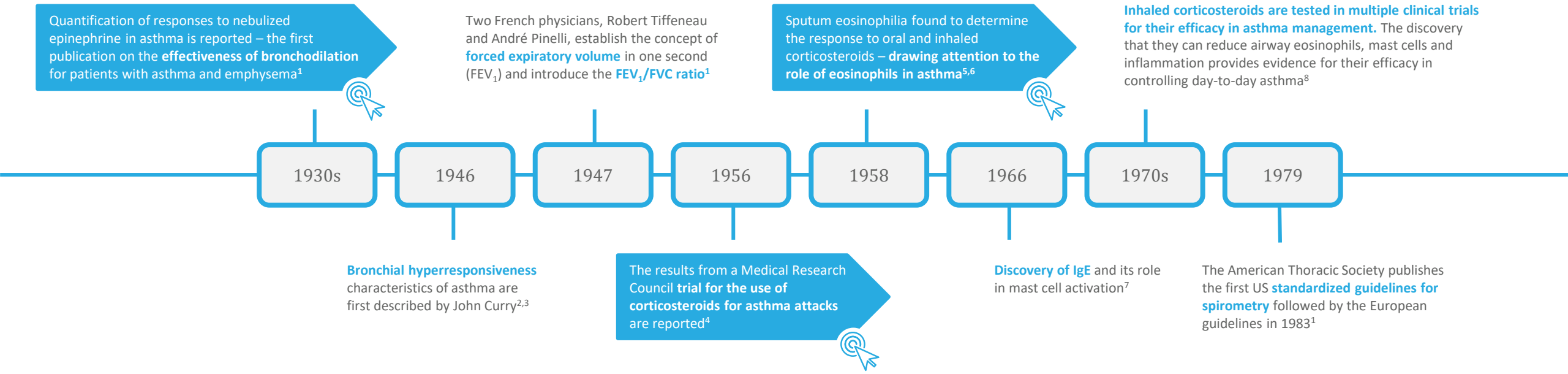
- The physiological era saw a move away from symptoms. During this era, asthma was considered as an acute disorder of episodic exacerbations, as a result of dysregulated airway neural control rather than a chronic inflammatory process



Approximate time period: 1930s–1970s

Abbreviations: FVC, forced vital capacity; IgE, immunoglobulin E; US, United States.

References: 1. Kouri A, et al. *Eur Respir Rev*. 2021;30:210081. 2. McFadden Jr ER. *Am J Respir Crit Care Med*. 2004;170:215-221. 3. Curry JJ. *J Clin Invest*. 1946;25(6):785-791. 4. *Lancet*. 1956;271(6947):803-806. 5. Brown HM. *Lancet*. 1958;2(7059):1245-1247. 6. Rupani H, et al. *J Inflamm Res*. 2021;14:4371-4397. 7. Diamant Z, et al. *Respir Med*. 2007;101(3):378-388. 8. Holgate ST. *Allergy Asthma Immunol Res*. 2010;2(3):165-171.

Key milestones in asthma management

The first report quantifying the effective use of a bronchodilator

In 1938, **Alvan Barach** notes diminished expiratory flow rates in adults with asthma and observes complete or partial reversal of these abnormalities with inhalation of nebulized epinephrine[1,2]

Increase in **inspiratory** velocity[1]

Increase in **expiratory** velocity[1]

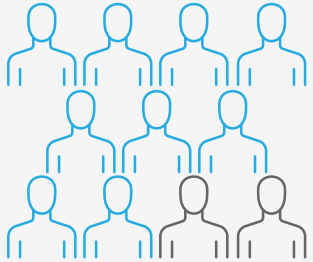
Slight **increase** in **vital capacity**[1]

Want to read more?

References: 1. Barach AL. *Ann Intern Med*. 1938;12(4):454-481. 2. Wu TD, et al. The history of pulmonary function testing. In: Kaminsky DA, Irvin CG, eds. Pulmonary Function Testing. *Principles and Practice*. Basel, Springer International Publishing. 2018;15-42.

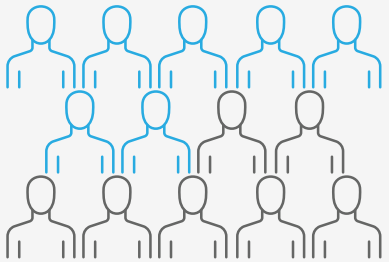
Efficacy of corticosteroids for asthmatic patients

In the 1950s, the introduction of systemic corticosteroid treatment in the UK is not straightforward due to an early and influential clinical trial sponsored by the **Medical Research Council** showing **little efficacy and highlighting a high potential for systemic toxicity.**[1,2]
During the three-month post-trial observation period:



9 out of 11 patients

in the **treatment group** reported having further attacks



7 out of 14 patients

in the **placebo group** reported having further attacks

Want to read more?

References: 1. *Lancet*. 1956;271(6947):803-806. 2. Pavord ID, et al. *Lancet*. 2018;391(10118):350-400.

Linking sputum eosinophilia with patient treatment response

Challenging the MRC trial, **Harry Morrow Brown** discovers that the **presence of eosinophils in the sputum** aligns with the **patients' response to corticosteroids**[1,2]

90 cases of chronic asthma treated with corticosteroids[1]

Relief of bronchospasm	Cases with eosinophilic sputum	Cases with a few or no eosinophils
Complete	56	1
Partial	7	3
Slight	-	7
No relief	-	16
Total	**63**	**27**

In this study, **100%** of patients with **eosinophilic sputum** had **complete or partial relief**

Want to read more?

Abbreviation: MRC, Medical Research Council.

References: 1. Brown HM. *Lancet*. 1958;2(7059):1245-1247. 2. Pavord ID, et al. *Lancet*. 2018;391(10118):350-400.

The 'Immunological' era

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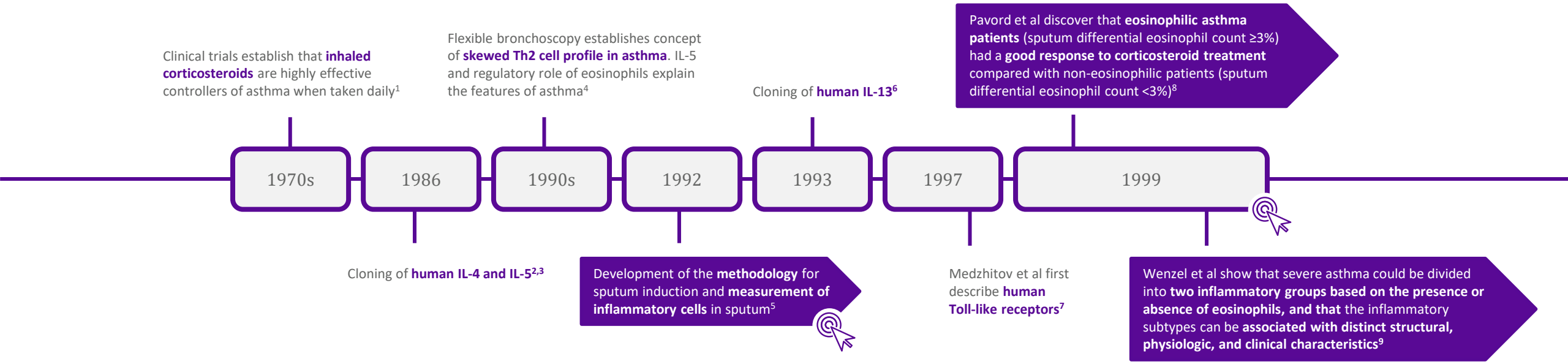
- This era saw the understanding of the inflammatory and immunologic nature of asthma grow, alongside awareness that chronic asthma could lead to airway remodeling identifiable with spirometry



Approximate time period: 1970s–1990s

Abbreviations: IL, interleukin; Th, T helper.

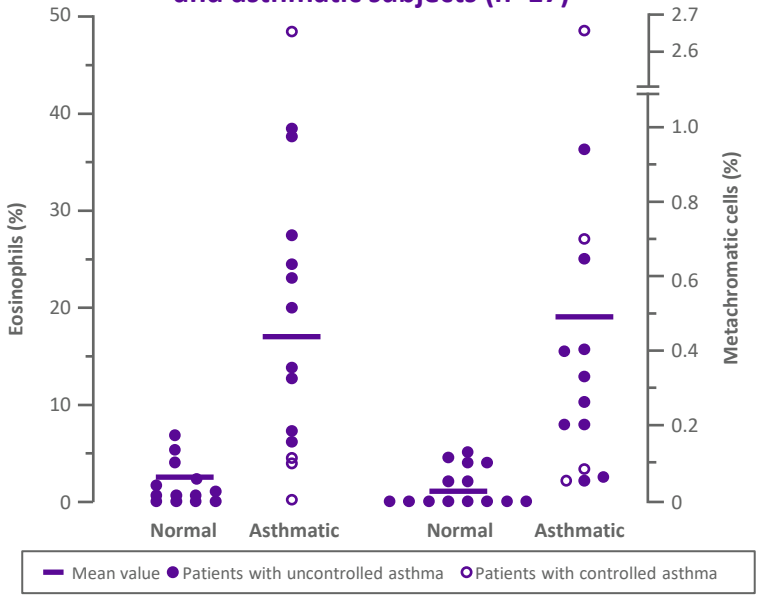
References: 1. Holgate ST. *Allergy Asthma Immunol Res*. 2010;2(3):165-171. 2. Yokota T, et al. *Proc Natl Acad Sci USA*. 1986;83(16):5894-5898. 3. Azuma C, et al. *Nucleic Acids Res*. 1986;14(22):9149-9158. 4. Diamant Z, et al. *Respir Med*. 2007;101(3):378-388. 5. Pin I, et al. *Thorax*. 1992;47:25-29. 6. Minty A, et al. *Nature*. 1993;362(6417):248-250. 7. Medzhitov R, et al. *Nature*. 1997;388(6640):394-397. 8. Pavord ID, et al. *Lancet*. 1999;353(9171):2213-2214. 9. Wenzel SE, et al. *Am J Respir Crit Care Med*. 1999;160(3):1001-1008.

Non-invasive measurement of airway inflammation

In the 1980s, the importance of persistent airway inflammation in the pathogenesis of asthma is becoming apparent. However, the type of inflammatory response is difficult to measure, with invasive methods required[1]

Isabelle Pin et al develop a non-invasive **measurement of airway inflammation** in asthmatic patients using **induced sputum cell counts**[2]

Differential cell counts of eosinophils and metachromatic cells in normal (n=17) and asthmatic subjects (n=17)



Adapted from Pin I, et al. *Thorax*. 1992;47:25-29.

Want to read more?

References: 1. Kirby JG, et al. *Am Rev Respir Dis*. 1987;136:379-383. 2. Pin I, et al. *Thorax*. 1992;47:25-29.

Eosinophilic asthma vs non-eosinophilic asthma

Two independent studies suggest that patients with severe asthma can be divided into **two distinct subgroups** based on the **presence or absence of eosinophils**[1,2]

- **Ian Pavord** et al show that patients with **non-eosinophilic asthma** have a **poor response to corticosteroids** compared to those with eosinophilic asthma[1]
- **Sally Wenzel** et al observe **distinct characteristics** of two pathologically different inflammatory groups of patients with **severe asthma** based on the **presence or absence of eosinophils**[2]

Non-eosinophilic asthma	
Definition	Absence of elevated eosinophil counts in blood or sputum (<3%)
Steroid response	Poor response to corticosteroids
Eosinophilic asthma	
Definition	Increased blood (>300/µL) or sputum eosinophil counts (≥3%)
Steroid response	Good response to corticosteroids

Want to read more?

References: 1. Pavord ID, et al. *Lancet*. 1999;353(9171):2213-2214. 2. Wenzel SE, et al. *Am J Respir Crit Care Med*. 1999;160(3):1001-1008.

The ‘Phenotypic’ era

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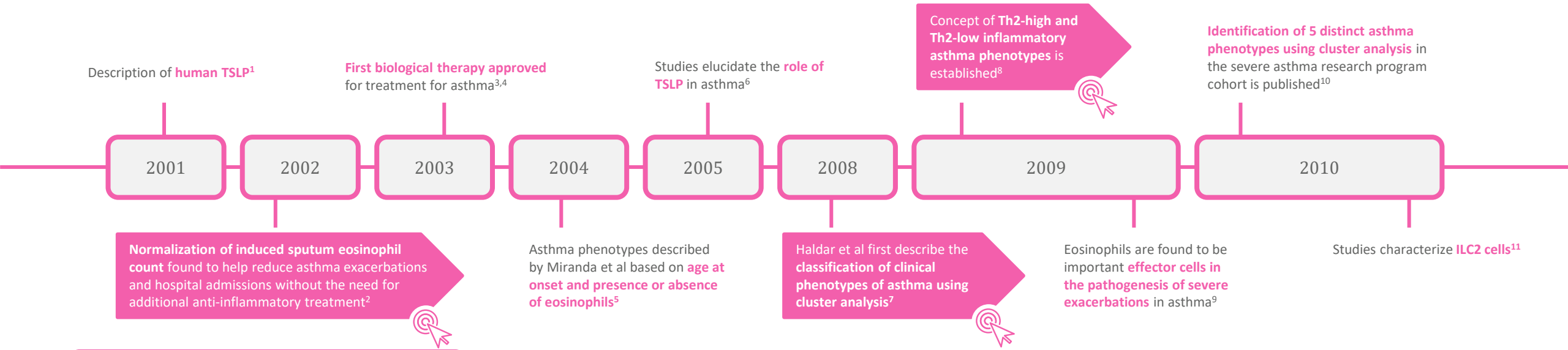
- This era saw the clustering of specific asthma phenotypes based on observable characteristics resulting from a combination of both environmental and hereditary influences



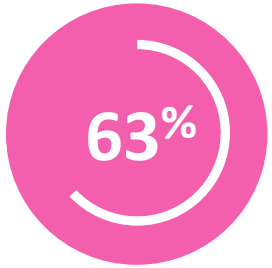
Approximate time period: 2000s–2010s

Abbreviations: ILC, innate lymphoid cell; Th, T helper; TSLP, thymic stromal lymphopoietin.

References: 1. Reche PA, et al. *J Immunol*. 2001;167(1):336-343. 2. Green RH, et al. *Lancet*. 2002;360(9347):1715-1721. 3. Pavord I, et al. *Eur Respir Rev*. 2019;28:190054. 4. Castillo JR, et al. *J Allergy Clin Immunol Pract*. 2017;5(4):918-927. 5. Miranda C, et al. *J Allergy Clin Immunol*. 2004;113(1):101-108. 6. West EE, et al. *Drug Discov Today Dis Mech*. 2012;9(3-4):10.1016/j.ddmec.2012.09.003. 7. Haldar P, et al. *Am J Respir Crit Care Med*. 2008;178(3):218-224. 8. Woodruff PG, et al. *Am J Respir Crit Care Med*. 2009;180(5):388-395. 9. Haldar P, et al. *N Engl J Med*. 2009;360:973-984. 10. Moore WC, et al. *Am J Respir Crit Care Med*. 2010;181(4):315-323. 11. Halim TY. *Int Immunol*. 2016;28(1):13-22.

Targeting eosinophilic inflammation to reduce asthma exacerbations

Ruth Green et al discover that by managing patients using the induced sputum eosinophil count vs standard management strategies[1*]:



Lower sputum eosinophil count over 12 months (p=0.002)

Patients experience significantly **fewer exacerbations** (p=0.01)

Fewer patients are admitted to hospital with asthma (p=0.047)

*Patients (n=74) were randomized to receive standard management (BTS group) or management by normalization of the induced sputum eosinophil count and reduction of symptoms (sputum group).

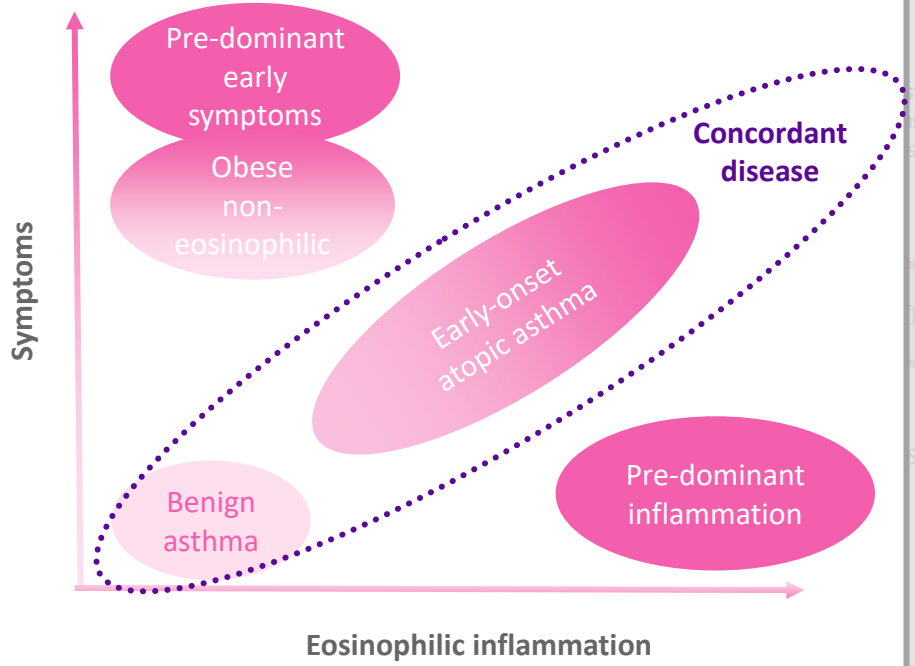
Want to read more?
Abbreviation: BTS, British Thoracic Society.
Reference: 1. Green RH, et al. *Lancet*. 2002;360(9347):1715-1721.

Identifying clinical phenotypes

Pranab Haldar et al identify clinical phenotypes using cluster analysis in asthmatic populations[1]

These can be plotted according to two clinically pertinent and modifiable dimensions of asthma[1]:

- **Relative expression of symptoms**
- **Eosinophilic inflammation**



Adapted from Haldar P, et al. *Am J Respir Crit Care Med*. 2008;178(3):218-224.

Want to read more?

Reference: 1. Haldar P, et al. *Am J Respir Crit Care Med*. 2008;178(3):218-224.

Asthma phenotyping based on Th2 inflammation

Woodruff et al show that asthma can be divided into **two distinct molecular phenotypes** defined by the degree of Th2 inflammation[1]

Prescott Woodruff et al observe that the patient subgroups (right) **differ significantly** (all $p<0.03$) in[1]:

- Expression of IL-5 and IL-13
- Airway hyperresponsiveness
- Serum IgE
- Blood and airway eosinophilia
- Subepithelial fibrosis
- Airway mucin gene expression

T2-High

- *Allergic, atopic*
- ***Eosinophilic***
- ***Steroid responsive***
- *Involve Th2 and ILC2 cells*[2]

T2-Low

- *Non-atopic*
- ***Non-eosinophilic***
- ***Poor steroid response***
- *Involve Th1 and Th17 cells*

Want to read more?

Abbreviations: IgE, immunoglobulin E; IL, interleukin; ILC, innate lymphoid cell; Th, T helper.

References: 1. Woodruff PG, et al. *Am J Respir Crit Care Med*. 2009;180(5):388-395. 2. Kuruvilla ME, et al. *Clin Rev Allergy Immunol*. 2019;56(2):219-233.

The ‘Endotypes’ era

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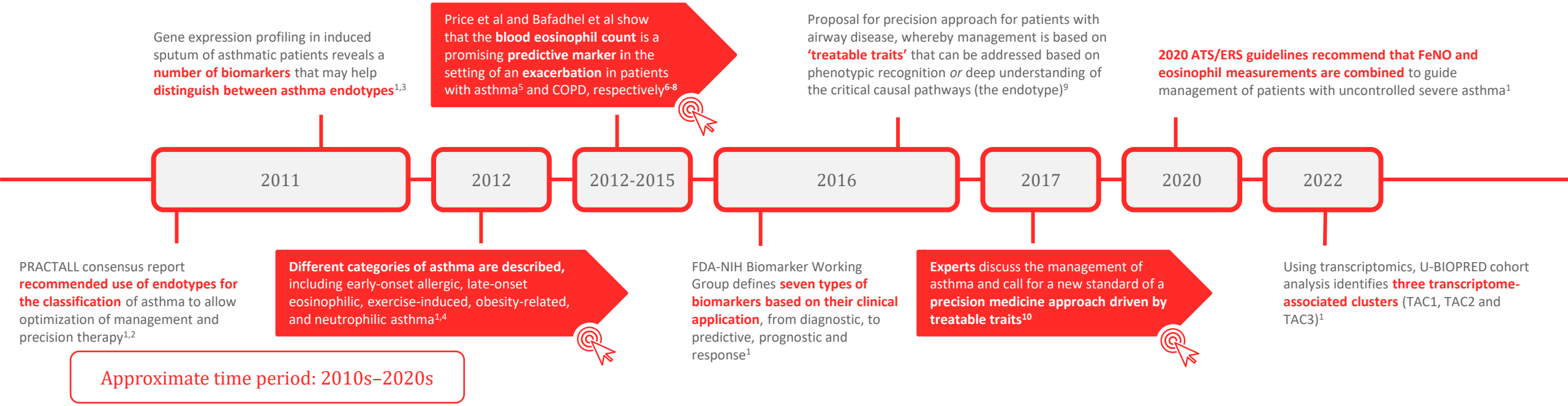
- This era saw an evolution of asthma classification via evaluation of the molecular mechanisms that drive a particular asthma phenotype. Asthma endotypes describe the specific pathophysiological mechanisms that drive asthma at a cellular level



Abbreviations: ATS, American Thoracic Society; COPD, chronic obstructive pulmonary disease; ERS, European Respiratory Society; FDA, Food and Drug Administration; FeNO, fractional exhaled nitric oxide; NIH, National Institute of Health; TAC, transcriptome associated clusters; U-BIOPRED, Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes.

References: 1. Porpodis K, et al. *J Pers Med*. 2022;12:1093. 2. Lötvall J, et al. *J Allergy Clin Immunol*. 2011;127(2):355-360. 3. Baines KJ, et al. *J Allergy Clin Immunol*. 2011;127:153-160.e1609. 4. Wenzel SE. *Nat Med*. 2012;18:716-725. 5. Price DB, et al. *Lancet Respir Med*. 2015;3(11):849-858. 6. Bafadhel M, et al. *Am J Respir Crit Care Med*. 2011;184:662-671. 7. Bafadhel M, et al. *Am J Respir Crit Care Med*. 2012;186:48-55. 8. Bafadhel M, et al. *Eur Respir J*. 2014;44:789-791. 9. Agusti A, et al. *Eur Respir J*. 2016;47:410-419. 10. Pavord ID, et al. *Lancet*. 2018;391(10118):350-400.

This era saw an evolution of asthma classification, via evaluation of the molecular mechanisms that drive a particular asthma

Linking biology to phenotypes — suggesting categories of asthma

Asthma phenotypes initially focused on combinations of clinical characteristics, but have evolved to link biology to phenotype (ie, endotype)[1]

	Clinical features	Pathobiology and biomarkers
Early-onset allergic	Allergic symptoms; mild to severe	Specific IgE; Th2 cytokines; thick SBM
Late-onset eosinophilic	Sinusitis; less allergic; often severe	Corticosteroid-refractory eosinophilia; IL-5
Exercise-induced	Mild; intermittent with exercise	Mast cell activation; Th2 cytokines; cysteinyl leukotrienes
Obesity-related	Symptomatic; airway hyperresponsiveness unclear	Lack of Th2 biomarkers; oxidative stress
Neutrophilic	Low FEV_1; more air trapping	Sputum neutrophilia; Th17 pathways; IL-8

Sally Wenzel highlights that future molecular and genetic-focused research may enhance our understanding of asthma phenotypes and lead to more targeted and personalized approaches to asthma therapy[1]

Want to read more?

Abbreviations: FEV_1, forced expiratory volume in one second; IgE, immunoglobulin E; IL, interleukin; ILC, innate lymphoid cell; SBM, subepithelial basement membrane; Th, T helper.

Reference: 1. Wenzel SE. *Nat Med*. 2012;18:716-725.

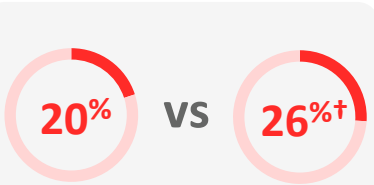
This era saw an evolution of asthma classification, via evaluation of the molecular mechanisms that drive a particular asthma

Using blood eosinophil count as a predictive biomarker

Studies in patients with COPD highlight that patients who present in similar ways can have considerable differences in their airway inflammation.[1,2] Additionally, these studies suggest that the heterogenicity seen with COPD patients can be defined using readily accessible biomarkers, such as blood eosinophil counts[1-4]

In the setting of an exacerbation, **Mona Bafadhel** et al show that **blood eosinophil counts** help identify patients with COPD who may **respond better to oral steroids**[4]

treatment failure rate in patients with a **blood eosinophil count ≥2%**, who did not receive oral steroids vs those who did.



treatment failure rate in patients with a **blood eosinophil count <2%**, who did not receive oral steroids vs those who did.

*Mean difference 55%, 95% CI: 38%–73%, p<0.001.[4]
†Mean difference 6%, 95% CI: -9%–27%, p=ns.[4]

Want to read more?

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disorder; ns, not significant.

References: 1. Pavord ID, et al. *Lancet*. 2018;391(10118):350-400. 2. Bafadhel M, et al. *Am J Respir Crit Care Med*. 2011;184:662-671. 3. Bafadhel M, et al. *Am J Respir Crit Care Med*. 2012;186:48-55. 4. Bafadhel M, et al. *Eur Respir J*. 2014;44:789-791.

This era saw an evolution of asthma classification, via evaluation of the molecular mechanisms that drive a particular asthma

Call for a new 'standard' approach to asthma management and treatment focusing on precision medicine

In a Lancet Commission, **expert clinicians and researchers** in asthma provide their view of where we are and where we need to go as a community to tackle the considerable public health problem of asthma[1]

Seven key recommendations from the Commission are:[1]

- A revolution in delivering precision medicine in asthma treatment
- Emerge from the age-associated and discipline-associated silos
- Zero tolerance for attacks
- Better research
- Test before treatment
- Move beyond a disease control approach towards prevention and disease modifying treatments
- Make the most of new opportunities in severe disease

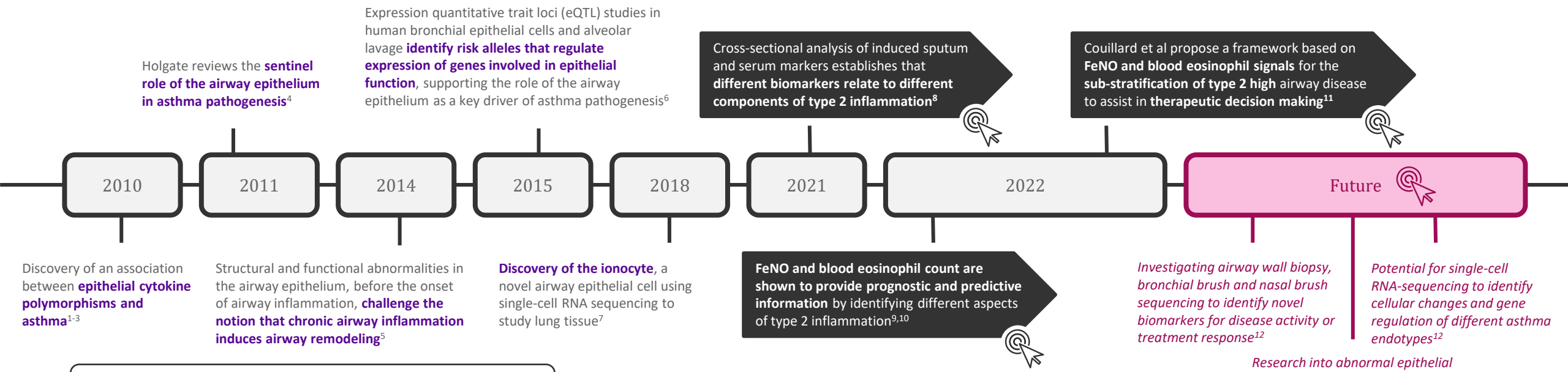
Want to read more?

Reference: 1. Pavord ID, et al. *Lancet*. 2018;391(10118):350-400.

The ‘Epithelial’ era*

EpiCentral
UNDERSTANDING THE CENTRAL ROLE OF THE EPITHELIUM IN SEVERE ASTHMA AND BEYOND

- Epithelial science is a new frontier in asthma research, and we are working to better characterize the key role of the airway epithelium and epithelial cytokines – such as thymic stromal lymphopoietin (TSLP), interleukin (IL)-33 and IL-25 – in triggering inflammation in asthma



Approximate time period: 2010–Present and beyond?

*The ‘Epithelial’ era is based on a current theoretical era of ongoing research focused on the epithelium. The views and opinions are those of AstraZeneca and key opinion leaders involved in the creation of this document.

Abbreviations: eQTL, expression quantitative trait loci; FeNO, fractional exhaled nitric oxide; IL, interleukin; RNA, ribonucleic acid; TSLP, thymic stromal lymphopoietin.

References: 1. Hunninghake GM, et al. *Allergy*. 2010;65:1566-1575. 2. Moffatt MF, et al. *N Engl J Med*. 2010;363:1211-1221. 3. Torgerson DG, et al. *Nat Genet*. 2011; 43:887-892. 4. Holgate ST. *Immunol Rev*. 2011;242:205-219. 5. Heijink IH, et al. *Clin Exp Allergy*. 2014;44(5):620-630. 6. Li X, et al. *Allergy*. 2015;70(10):1309-1318. 7. Plasschaert LW, et al. *Nature*. 2018;560(7718):377-381. 8. Couillard S, et al. *Am J Respir Crit Care Med*. 2021;204:731-734. 9. Couillard S, et al. *ERJ Open Res*. 2021;8(1):00570-2021. 10. Couillard S, et al. *Thorax*. 2022;77(2):199-202. 11. Couillard S, et al. *Respirology*. 2022;27:573-577. 12. Heijink IH, et al. *Allergy*. 2020;75(8):1902-1917.

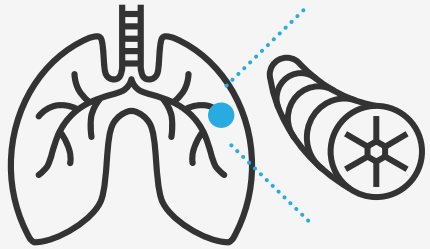
Key milestones in asthma management

Epithelial science is a new frontier in asthma research, and we are working to better characterize the key role of the airway

Linking FeNO and blood eosinophils to different compartments of inflammation

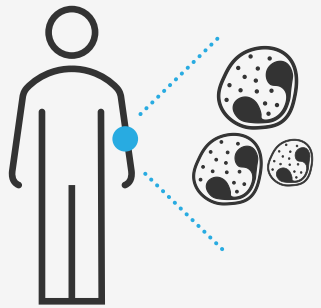
Simon Couillard et al uncover a relationship between fractional exhaled nitric oxide (FeNO), blood eosinophils, and various biomarkers of airway-specific and systemic inflammation, including alarmins, chemokines and cytokines[1]

These findings imply that **FeNO** and **blood eosinophils** relate to **different components** and **compartments of type 2 inflammation**[1]



FeNO reflects airway type 2 activity and the chemotactic pull in the **epithelium**

AND



Blood eosinophils reflect the systemic pool of available effector cells and circulating IL-5

Want to read more?

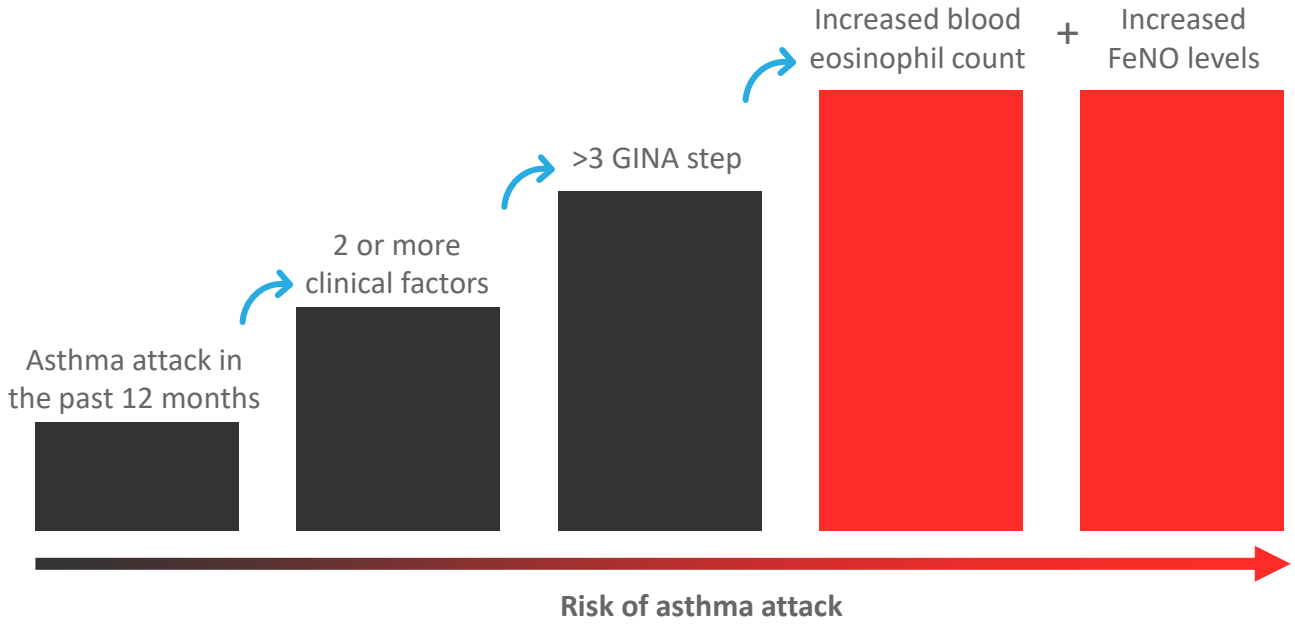
Abbreviations: FeNO, fractional exhaled nitric oxide; IL, interleukin.

Reference: 1. Couillard S, et al. *Am J Respir Crit Care Med*. 2021;204:731-734.

*The 'Epithelial' era is based on a current theoretical era of ongoing research focused on the epithelium. The views and opinions are those of AstraZeneca and key opinion leaders involved in the creation of this document.

Predicting the risk of asthma attacks with two biomarkers from different compartments: FeNO and blood eosinophil count

Using biomarker-stratified attack rates from the control arms of several clinical trials (n=3051), **Simon Couillard** et al propose the **prototype Oxford Asthma Attack Risk Scale (ORACLE)** that shows potential to **predict asthma attacks** based on **blood eosinophil count** and **FeNO**[1,2]



Adapted from Couillard S, et al. *Thorax*. 2022;77(2):199-202.

Want to read more?

Abbreviations: FeNO, fractional exhaled nitric oxide; ORACLE, Oxford Asthma Attack Risk Scale.

References: 1. Couillard S, et al. *Thorax*. 2022;77(2):199-202. 2. Couillard S, et al. *ERJ Open Res*. 2021;8(1):00570-2021.

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Epithelial science is a new frontier in asthma research, and we are working to better characterize the key role of the airway

A 'bomb' (blood eosinophils) meets a 'magnet' (FeNO)[1]

Simon Couillard *et al.* outline potential **features of 'magnet' and 'bomb' patients with T2-high asthma**[1]:

Bomb-driven patients		Magnet-driven patients
Late	**Onset**	Early
No	**Allergy**	Yes
Less	**AhR**	More
Less atopic CRSwNP, EGPA	**Associated co-morbidities**	Eczema, atopic rhinitis/CRSwNP
Blood eosinophil > FeNO	**Biomarker signal**	FeNO signal > blood eosinophil

Adapted from Couillard S, et al. *Respirology*. 2022;27(8):573-577.

This may lead to the possibility for **precision medicine**, and the selecting of the most appropriate treatment based on the patient '**magnet'/'bomb' biomarker** profiles[1]

Want to read more?

Abbreviations: AhR, airway hyperresponsiveness; CRSwNP, chronic rhinosinusitis with nasal polyps; EGPA, eosinophilic granulomatosis with polyangiitis; FeNO, fractional exhaled nitric oxide; T2, type 2.

Reference: 1. Couillard S, et al. *Respirology*. 2022;27(8):573-577.

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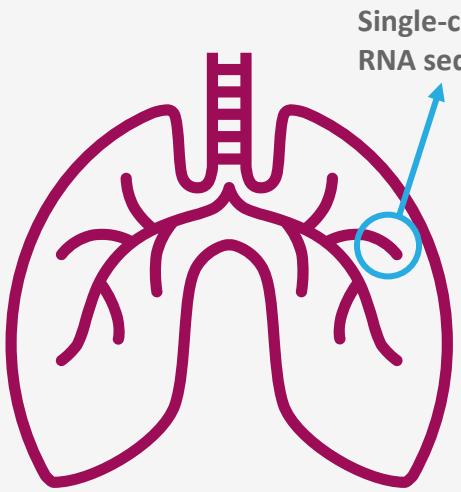
Further insights into asthma and role of the epithelium may come from technology advances

Abnormalities in the airway epithelial barrier play a **crucial role** in the sensitization to allergens and **pathogenesis of asthma**[1]

The exact mechanisms by which the expression of epithelial susceptibility genes translates into a functionally altered response to environmental risk factors of asthma are still unknown[1]

Insight into the epithelial barrier in asthma using **single-cell RNA sequencing (scRNA-seq)** holds promise for identifying patients likely to benefit from **epithelial-focused therapies** and finding **targets for novel therapies** aimed at correcting dysfunctional epithelial barrier[1]



Adapted from Heijink IH, et al. *Allergy*. 2020;75(8):1902-1917.

Want to read more?

Abbreviations: RNA, ribonucleic acid; scRNA-seq, single-cell RNA sequencing.

Reference: 1. Heijink IH, et al. *Allergy*. 2020;75(8):1902-1917.

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Key reference sources (1/2)

EpiCentral
UNDERSTANDING THE CENTRAL ROLE OF THE EPITHELIUM IN SEVERE ASTHMA AND BEYOND

To read more about some of the key milestones in the asthma timeline, click the citation below:

Prescientific era

1. Marketos SG & Ballas CN. *J Asthma*. 1982;19(4):263-269.
   The origin of the term asthma in Greek literature
2. Valent P, et al. *J Innate Immun*. 2016;8:111-120.
   Paul Ehrlich's contributions to science including cell staining and the concept of magic bullets
3. Rackemann FM. *Arch Intern Med (Chic)*. 1918;12:517-552.
   First publication that establishes the terms intrinsic and extrinsic asthma
4. Rackemann FM. *Am J Med*. 1947;3(5):601-606.
   Further classification of intrinsic and extrinsic asthma

Physiological era

1. *Lancet*. 1956;271(6947):803-806.
   Results of the MRC trial investigating the use of corticosteroids for patients with asthma
2. Brown HM. *Lancet*. 1958;2(7059):1245-1247.
   This study highlights the link between eosinophilic sputum and the patient response to treatment
3. Rupani H, et al. *J Inflamm Res*. 2021;14:4371-4397.
   This review discusses the recent insights into the management of inflammation in asthma

Immunological era

1. Pin I, et al. *Thorax*. 1992;47:25-29.
   Isabelle Pin's study on the use of induced sputum cell counts to investigate airway inflammation in asthma
2. Pavord ID, et al. *Lancet*. 1999;353(9171):2213-2214.
   This study highlights different treatment responses depending on the presence of eosinophilic airway inflammation
3. Wenzel SE, et al. *Am J Respir Crit Care Med*. 1999;160(3):1001-1008.
   This study establishes various characteristics of non-eosinophilic and eosinophilic asthma

Key reference sources (2/2)

EpiCentral
UNDERSTANDING THE CENTRAL ROLE OF THE EPITHELIUM IN SEVERE ASTHMA AND BEYOND

To read more about some of the key milestones in the asthma timeline, click the citation below:

Phenotypic era

1. Green RH, et al. *Lancet*. 2002;360(9347):1715-1721.
   This study discusses the positive impact of managing patients using the induced sputum eosinophil count
2. Haldar P, et al. *Am J Respir Crit Care Med*. 2008;178(3):218-224.
   This study identifies clinical phenotypes using cluster analysis in asthmatic populations
3. Woodruff PG, et al. *Am J Respir Crit Care Med*. 2009;180(5):388-395.
   This study highlights two distinct molecular phenotypes defined by Th2 (low or high) inflammation

Endotype era

1. Wenzel SE. *Nat Med*. 2012;18:716-725.
   This review outlines various categories of asthma that begin to link phenotypes to the underpinning biology (i.e. endotypes)
2. Bafadhel M, et al. *Eur Respir J*. 2014;44:789-791.
   This study highlights the use of the blood eosinophil count to possibly identify patient treatment responses
3. Pavord ID, et al. *Lancet*. 2018;391(10118):350-400.
   This Commission provides a detailed expert view of the current and future landscape of asthma

Epithelial era*

1. Couillard S, et al. *Am J Respir Crit Care Med*. 2021;204:731-734.
   This study connects FeNO and blood eosinophils with biomarkers and compartments of airway inflammation
2. Couillard S, et al. *Thorax*. 2022;77(2):199-202.
   This study outlines a proposed prototype risk scale (ORACLE) to predict asthma attacks
3. Couillard S, et al. *ERJ Open Res*. 2021;8(1):00570-2021.
   This study suggests a potential theragnostic utility of the ORACLE scale using trial-level data
4. Couillard S, et al. *Respirology*. 2022;27(8):573-577.
   This commentary details a sub-stratification of asthma based on 'bombs' (blood eosinophils) and 'magnets' (FeNO)
5. Heijink IH, et al. *Allergy*. 2020;75(8):1902-1917.
   This review focusses on insights and future research into the role of the airway epithelium in asthma

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