EHA&EuroBloodNet Spotlight on Hypereosinophilic Syndrome

Eosinophils, Hypereosinophilia and Hypereosinophilic Syndromes

Florence ROUFOSSE, MD, PhD

Hôpital Universitaire de Bruxelles – ERASME
Université Libre de Bruxelles

Co-funded by
the Health Programme
of the European Union

EHA EUROPEAN HEMATOLOGY ASSOCIATION

European Reference Network
for rare or low prevalence complex diseases
Network Hematological Diseases (ERN EuroBloodNet)

Practical issues before starting

- ✓ 30 min presentation + 15 min Q&A session
- ✓ Microphones will be muted by host to avoid back noise
- ✓ Please, stop your video to improve internet connexion
- ✓ Send your questions during the presentation through the chat, they will be gathered and answered after the presentations.

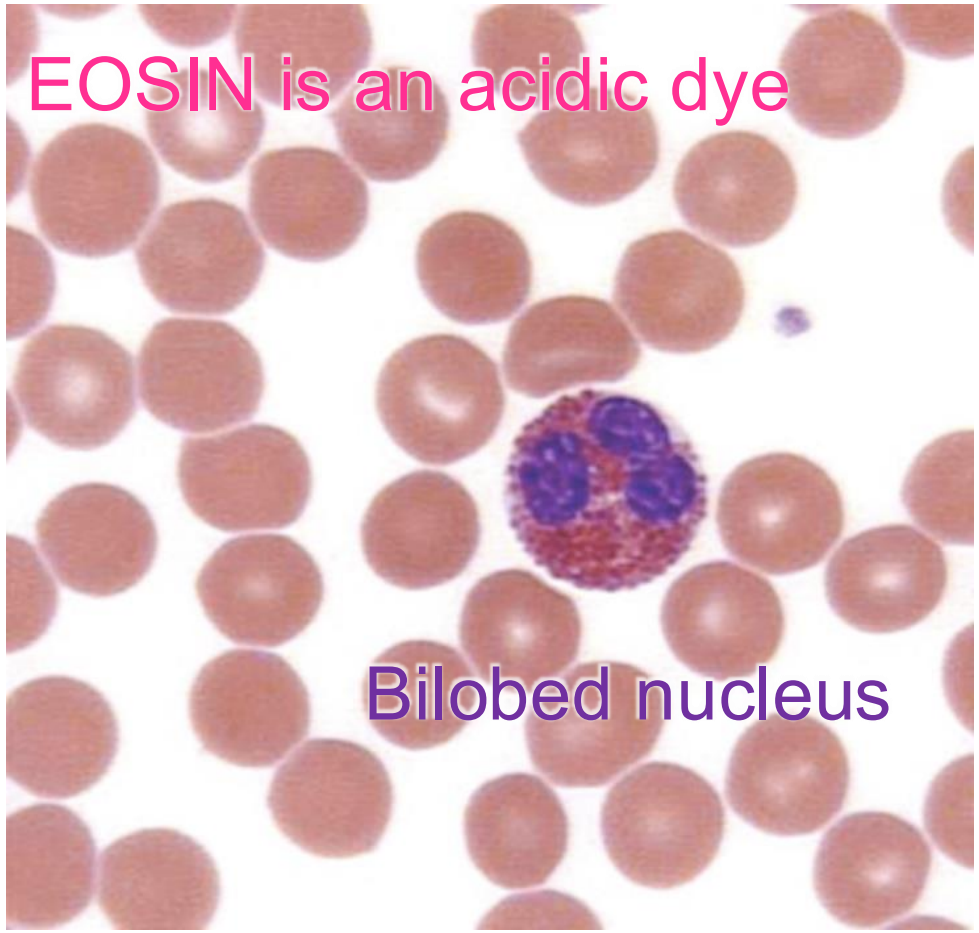
Learning objectives of the webinar

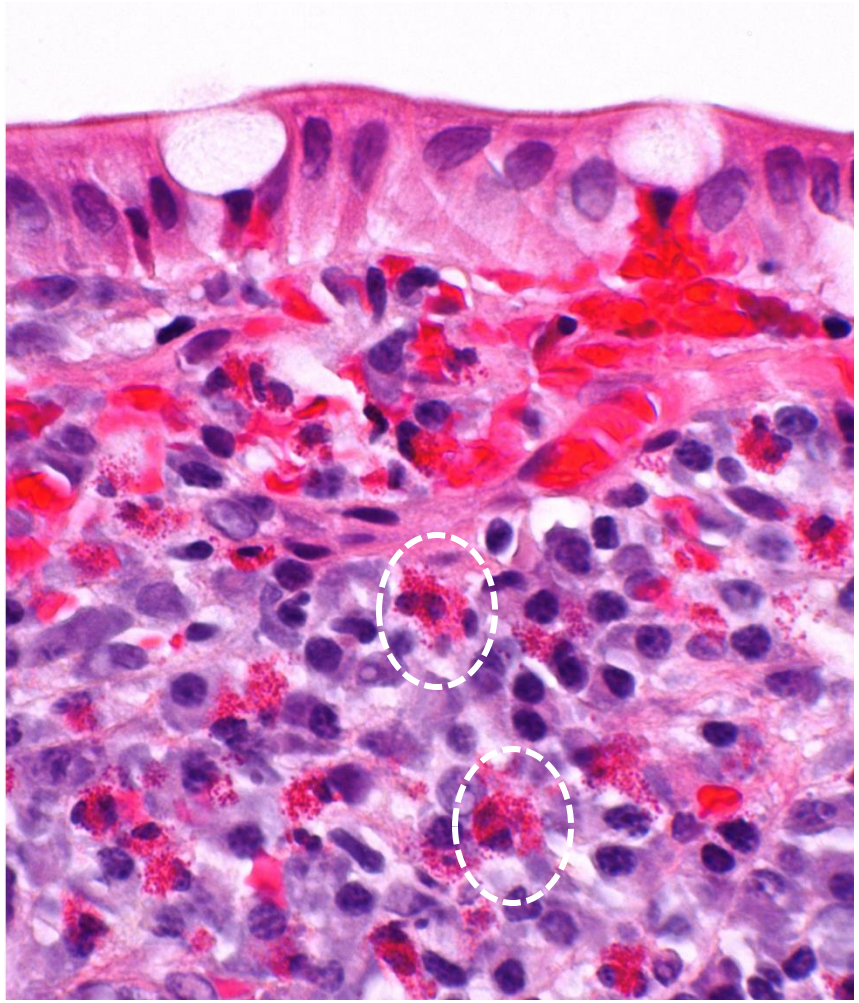
1. Eosinophil biology: what drives eosinophil expansion and activation
2. Mechanisms of eosinophil-mediated damage
3. Putative physiological and homeostatic roles of eosinophils
4. Definition of Hypereosinophilia and Hypereosinophilic syndrome (HES)
5. Common causes of hypereosinophilia
6. Target organ damage and dysfunction in HES
7. Classification of HES variants (pathogenic et clinical)

Conflicts of interest

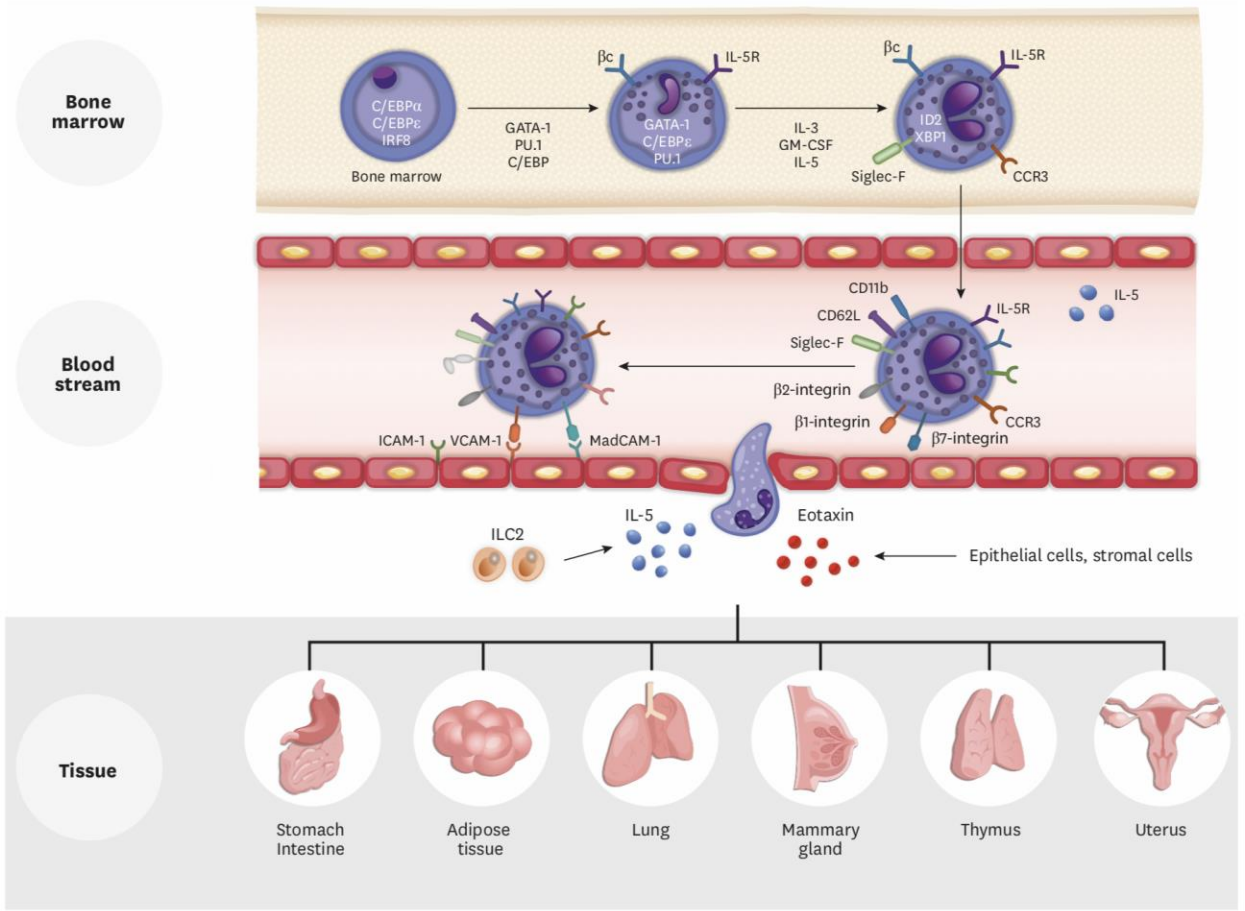
Consultancy and/or speaker fees from GlaxoSmithKline, Astra Zeneca, Menarini, Merck.

Introducing the eosinophil





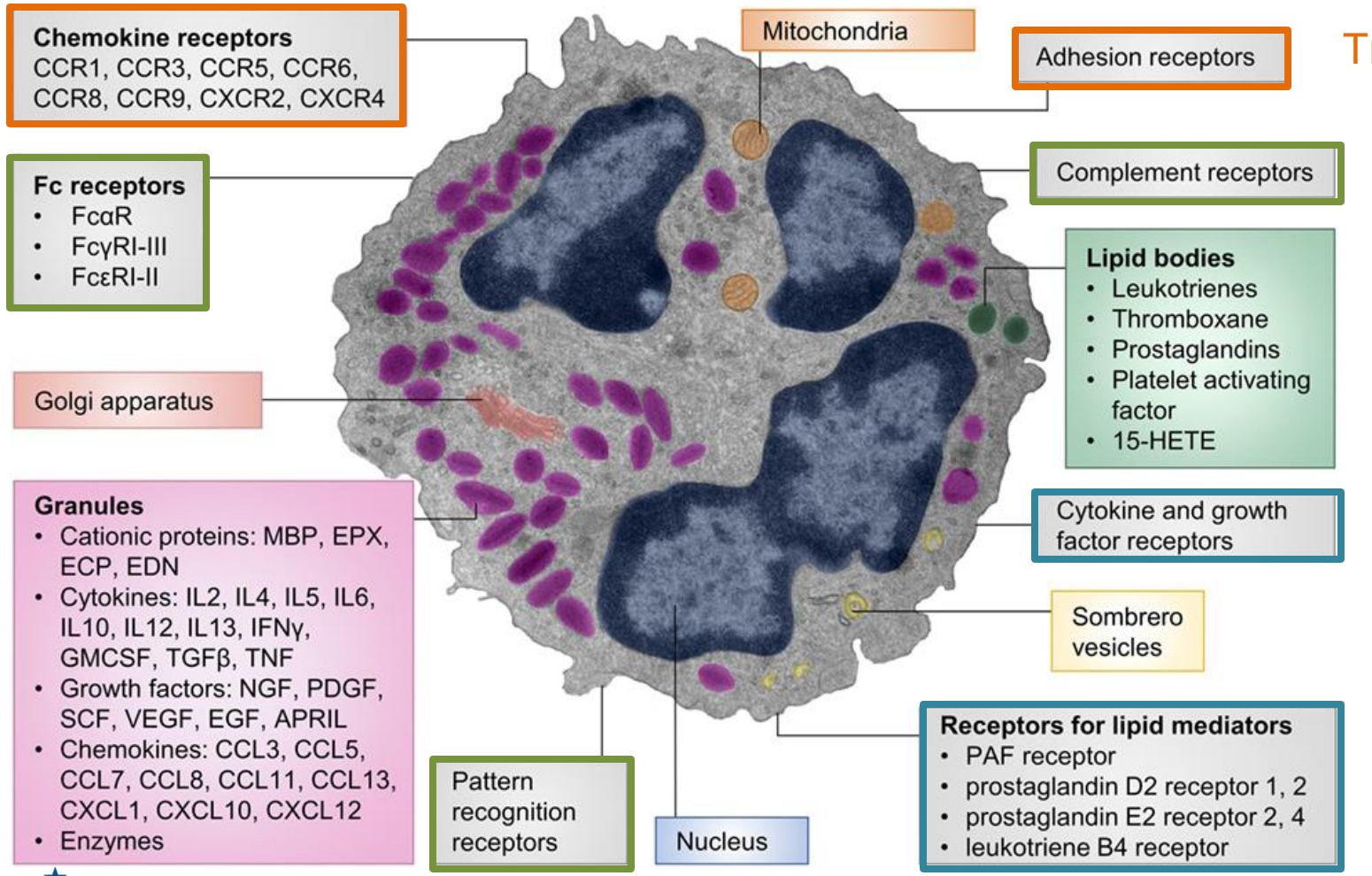
Eosinophil life cycle and homing



Kim and Jung. Immune Netw 2020; 20(3):e24.

Eosinophil Biology - Receptors

Innate immunity



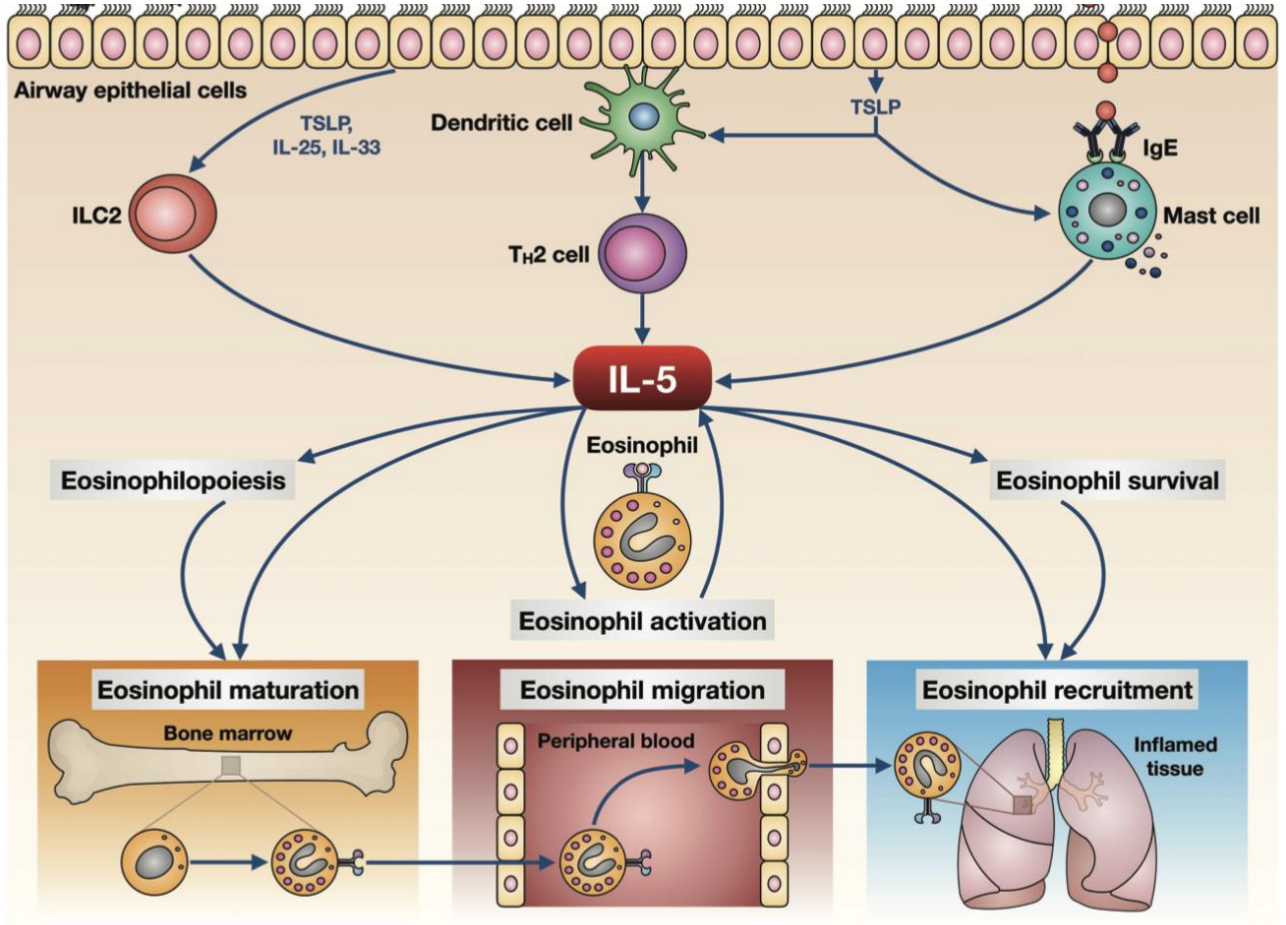
Trafficking

IL-5Rα

ST2 (IL-33R)

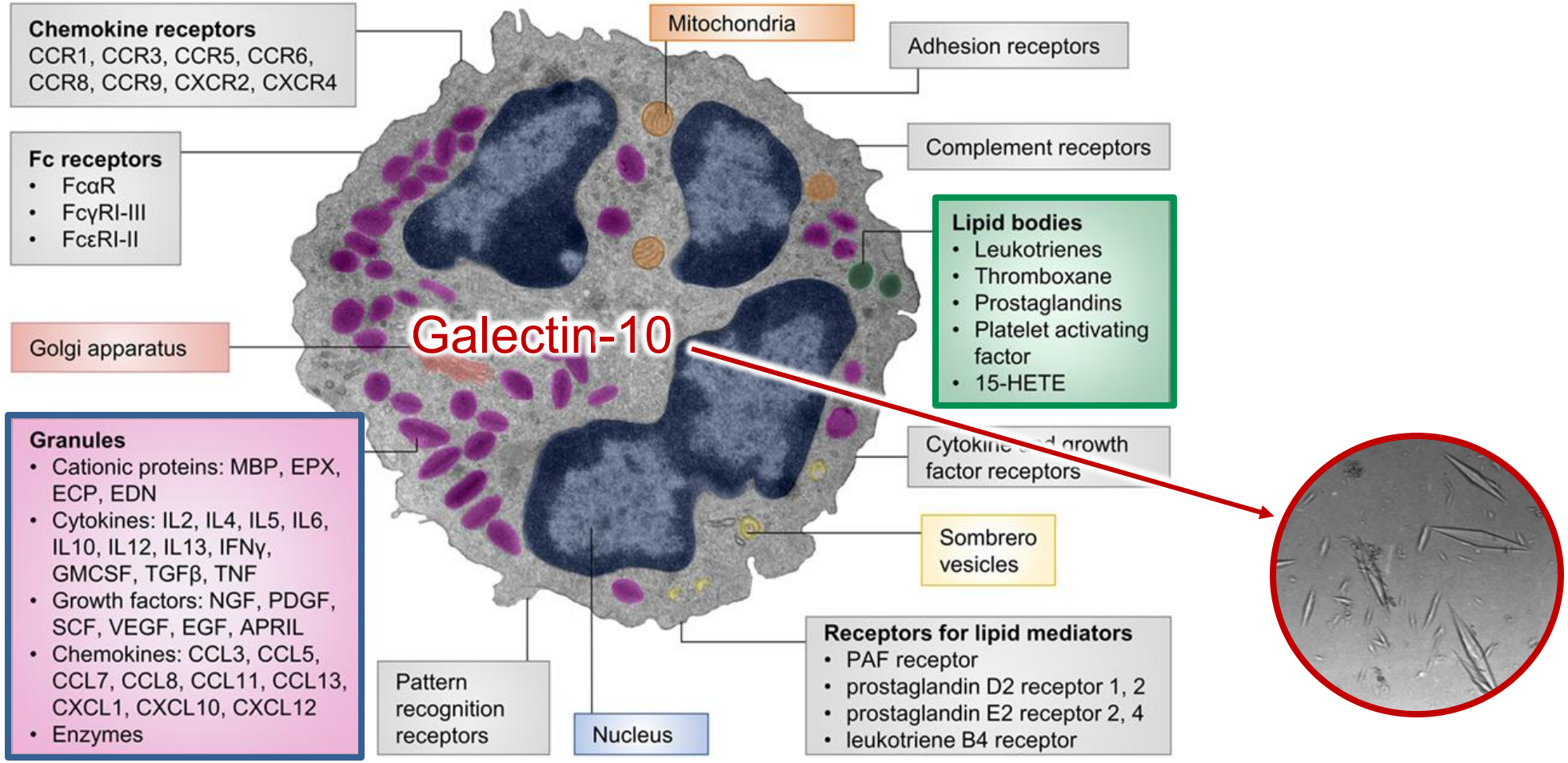
Diny N et al. Front Immunol, 27 April 2017.

IL-5 in Eosinophil Development and Life Cycle



Pellaia et al. Front Physiol 2019; 10: 1514.

Eosinophil Mediators



European Reference Network
for rare or low prevalence complex diseases
Network Hematological Diseases (ERN EuroBloodNet)

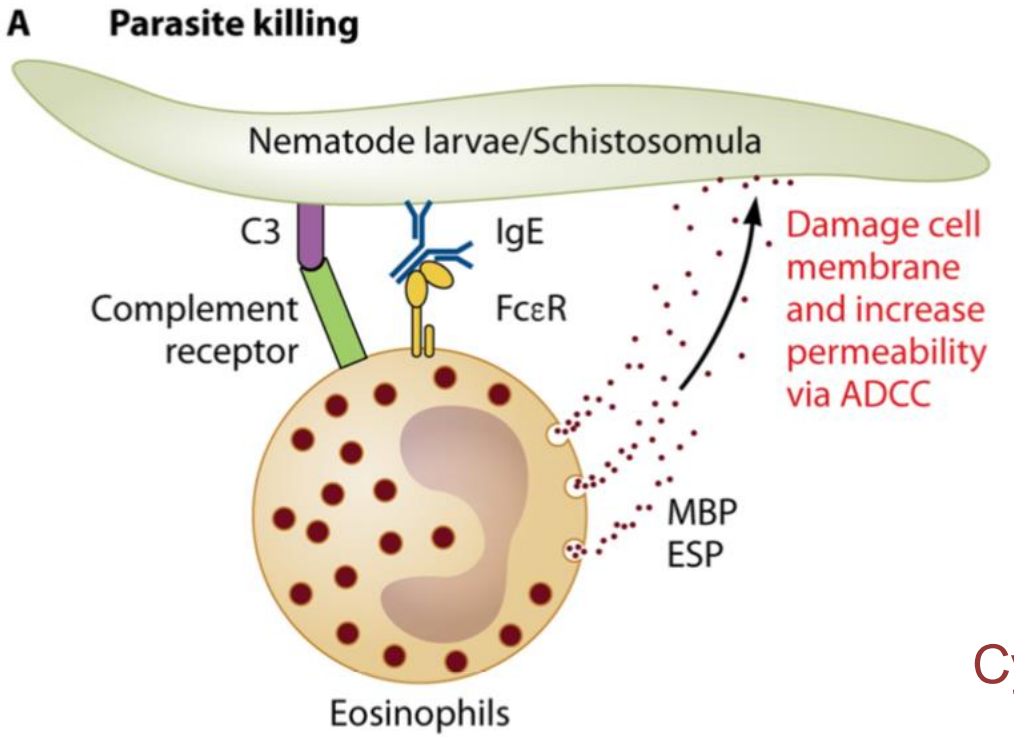
EHA EUROPEAN HEMATOLOGY ASSOCIATION

Webinars
EuroBloodNet

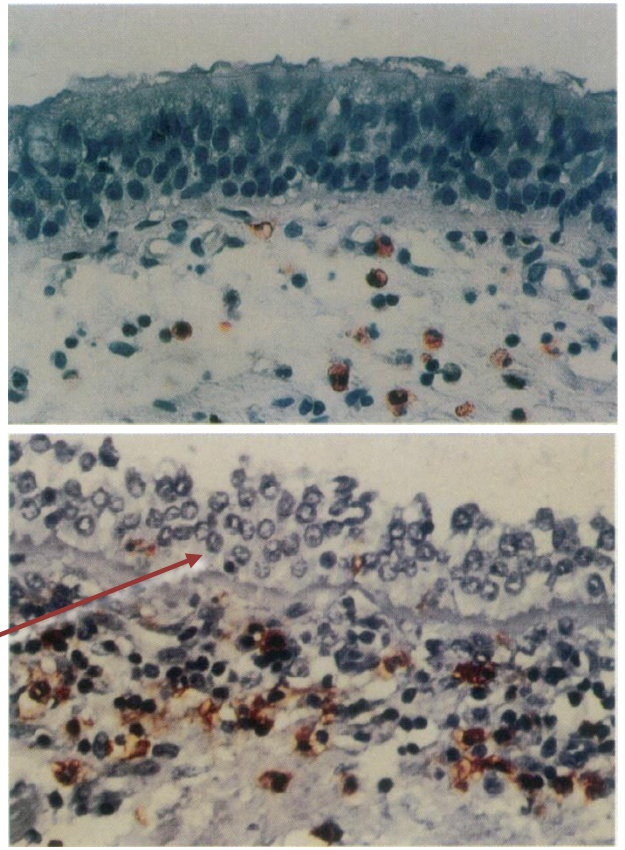
Diny N et al. Front Immunol, 27 April 2017.

What do Eosinophils do ? Historically…

They help us combat worms



They damage tissue in allergy

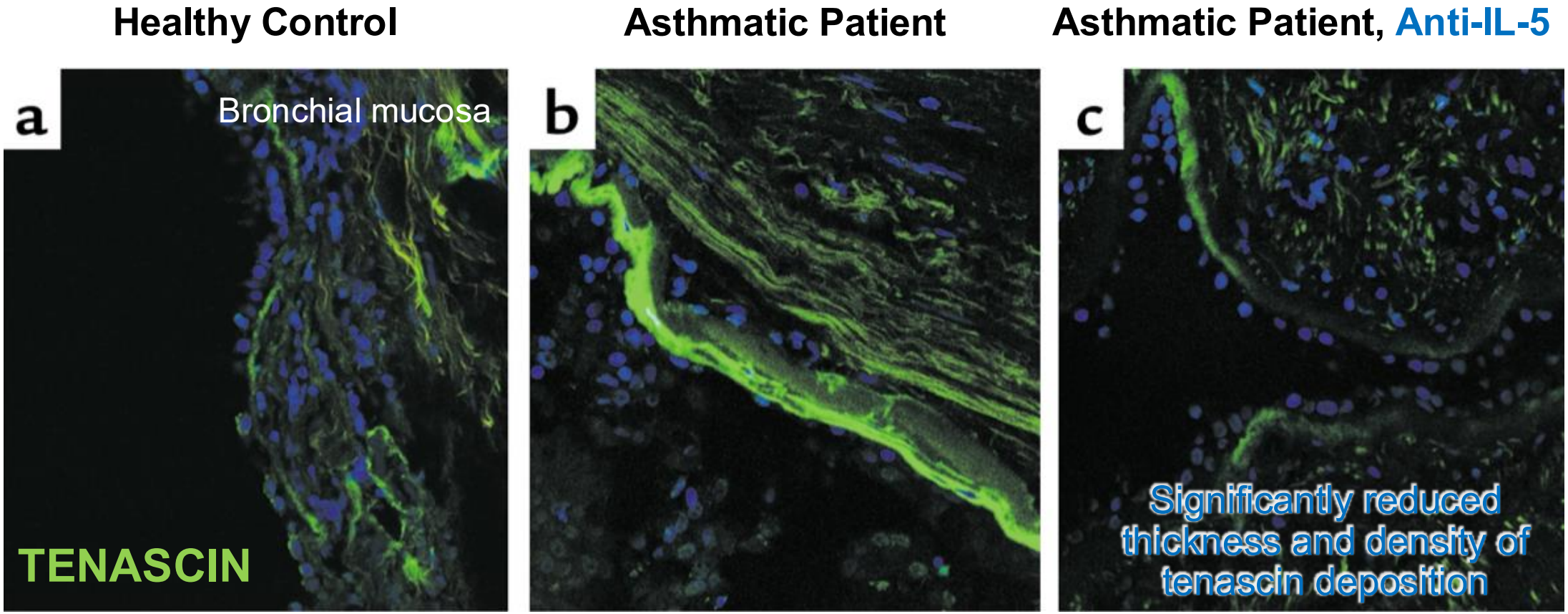


ECP stain

Cytotoxicity

Ariyaratne and Finney. Infection & Immunity 2019; 87(10):1-15. Bousquet et al. N Engl J Med 1990; 323, 1033–1039.

Eosinophils in asthma: ECM proteins and Remodelling



European Reference Network for rare or low prevalence complex diseases

Network Hematological Diseases (ERN EuroBloodNet)

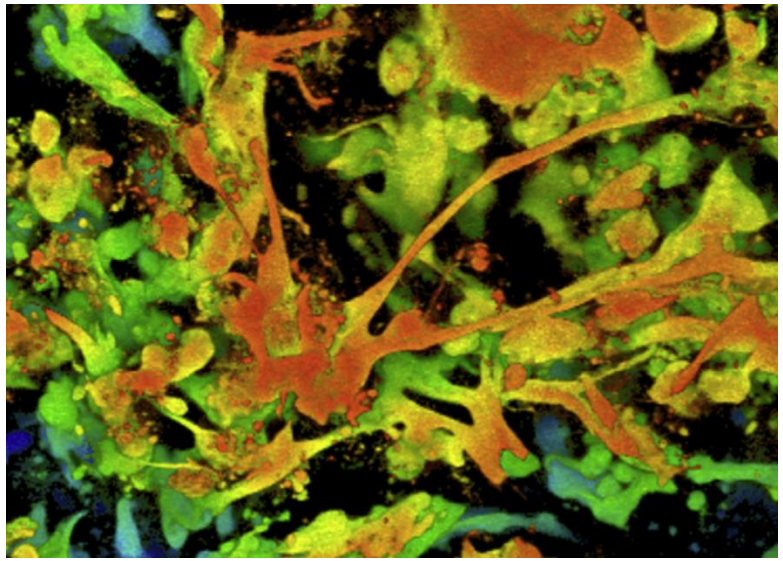
EHA EUROPEAN HEMATOLOGY ASSOCIATION

Webinars EuroBloodNet

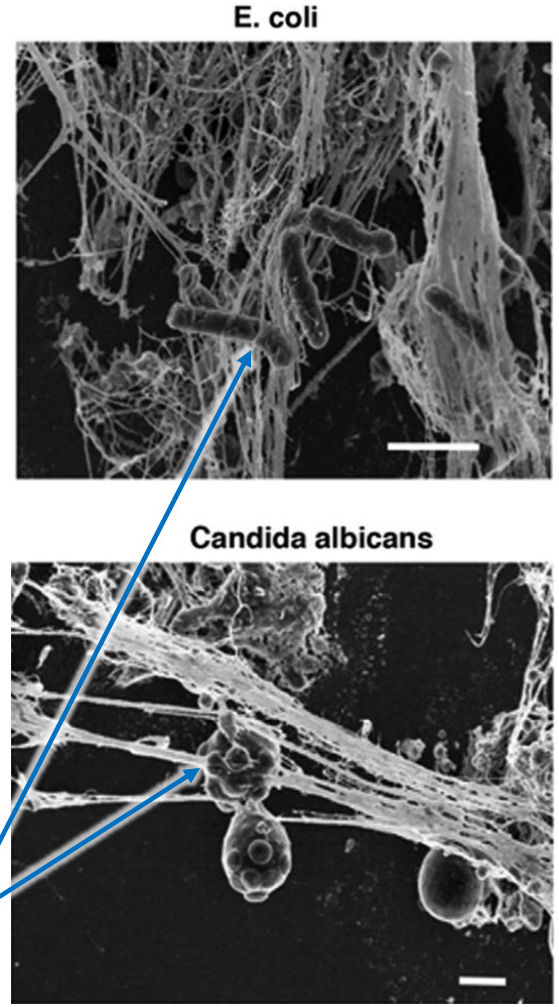
Flood-Page et al. J Clin Invest. 2003;112:1029.

Eosinophils in airway disease: EETosis, CLC, and mucus

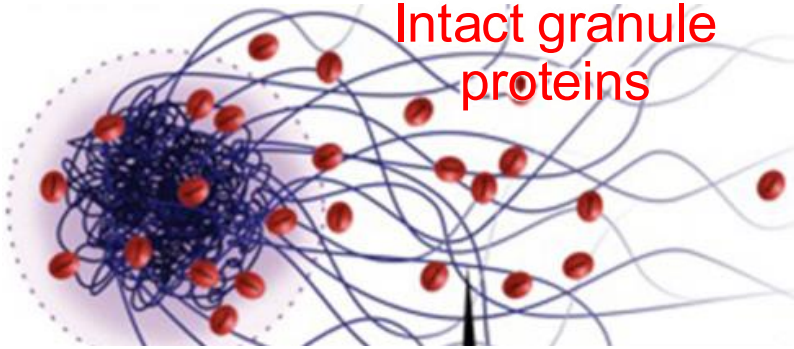
DNA Extracellular traps



DNA filaments released upon cytolytic death



Adhesive surfaces



European Reference Network for rare or low prevalence complex diseases

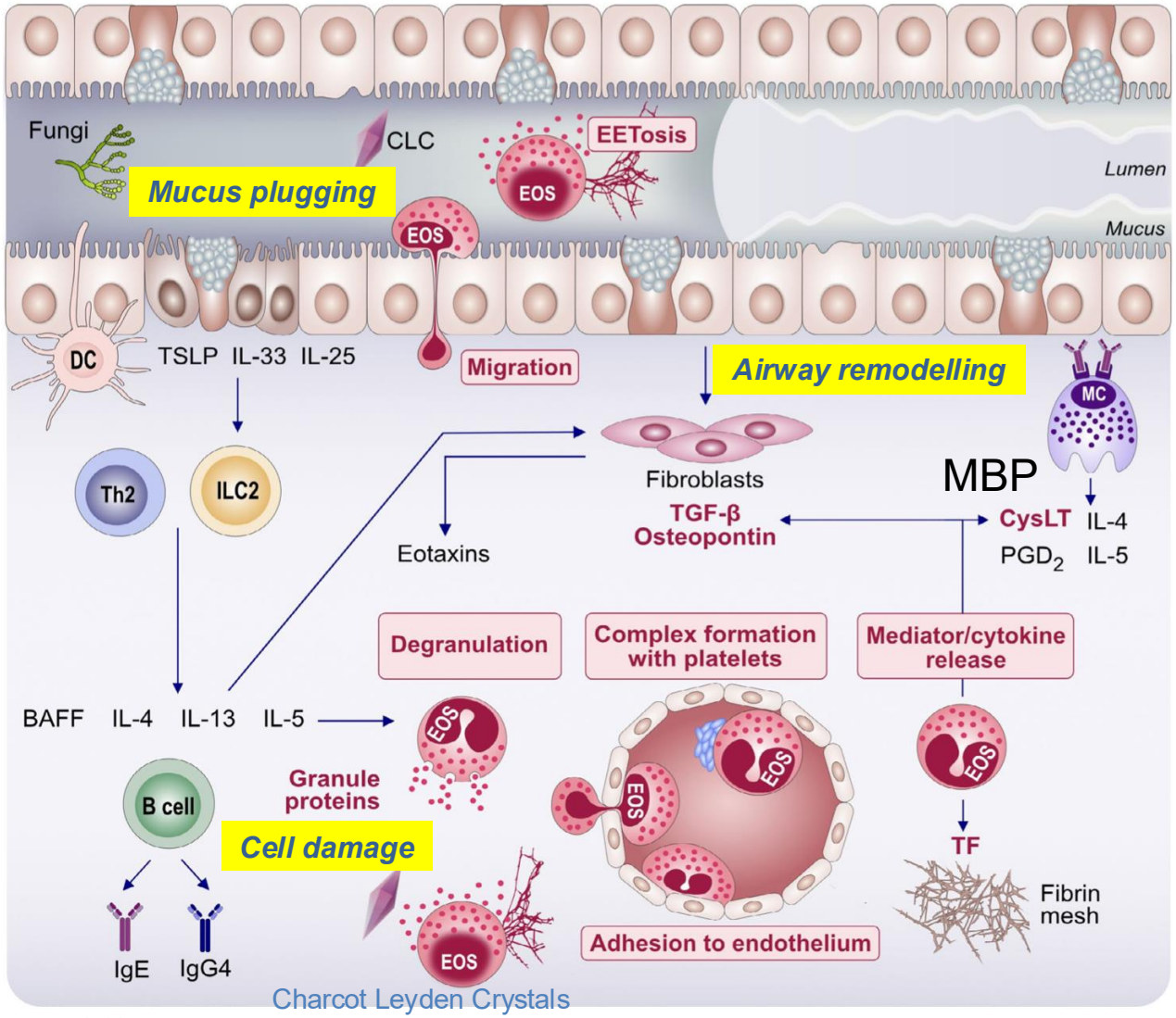
Network Hematological Diseases (ERN EuroBloodNet)

EHA EUROPEAN HEMATOLOGY ASSOCIATION

Webinars EuroBloodNet

Ueki et al, J Allergy Clin Immunol 2016;137:258. Persson et al, Science 2019; 364(6442): eaaw4295. . Mukherjee et al. Front Immunol 2018; 9.

Eosinophils in asthma … Nowadays



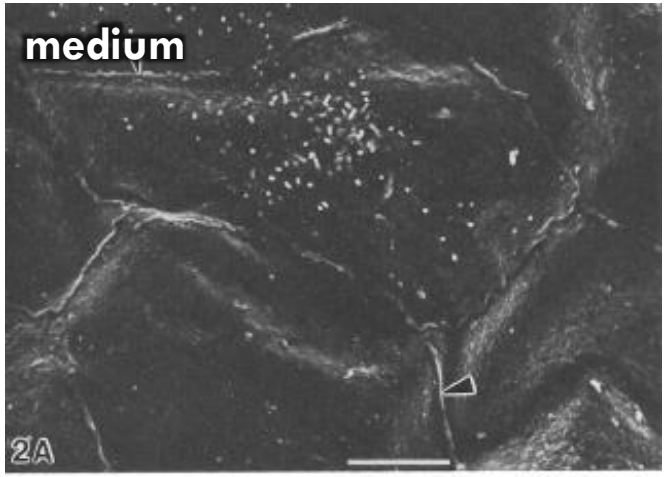
European Reference Network
for rare or low prevalence complex diseases
Network Hematological Diseases (ERN EuroBloodNet)

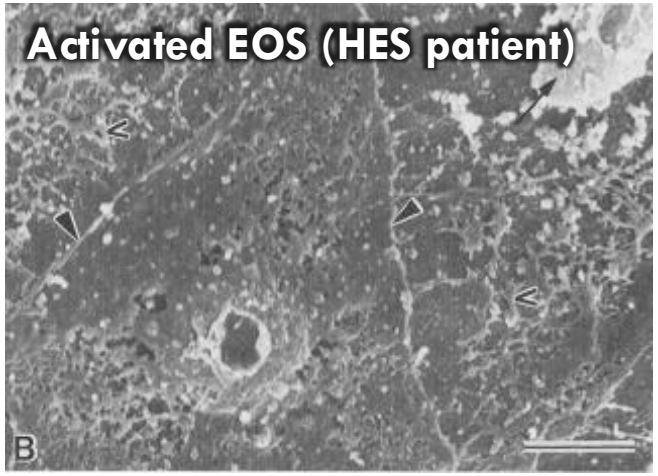
EHA ASSOCIATION

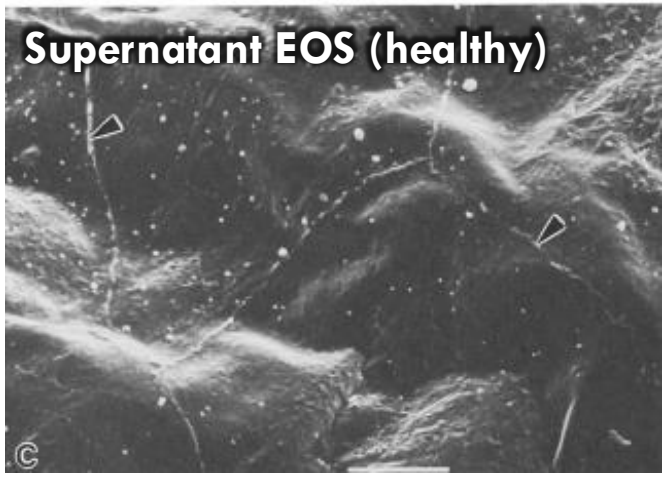
Webinars
EuroBloodNet

Asano et al, Allergy. 2020;75:3087–3099.

Direct role of eosinophils in tissue damage

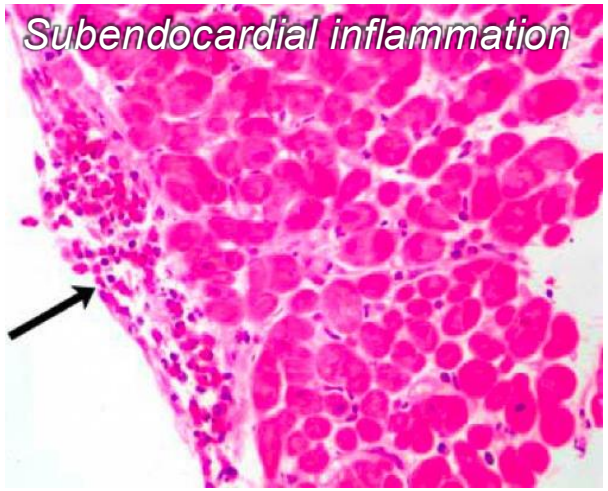


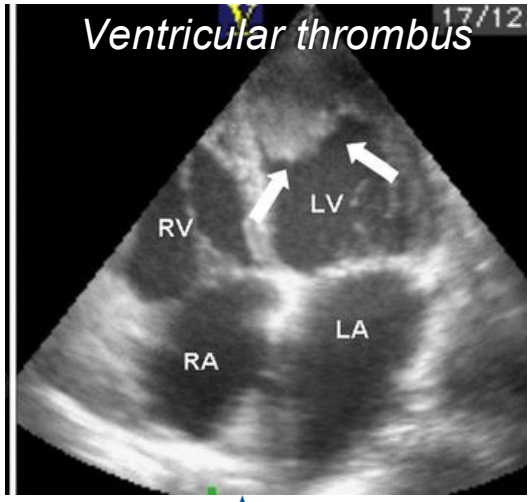


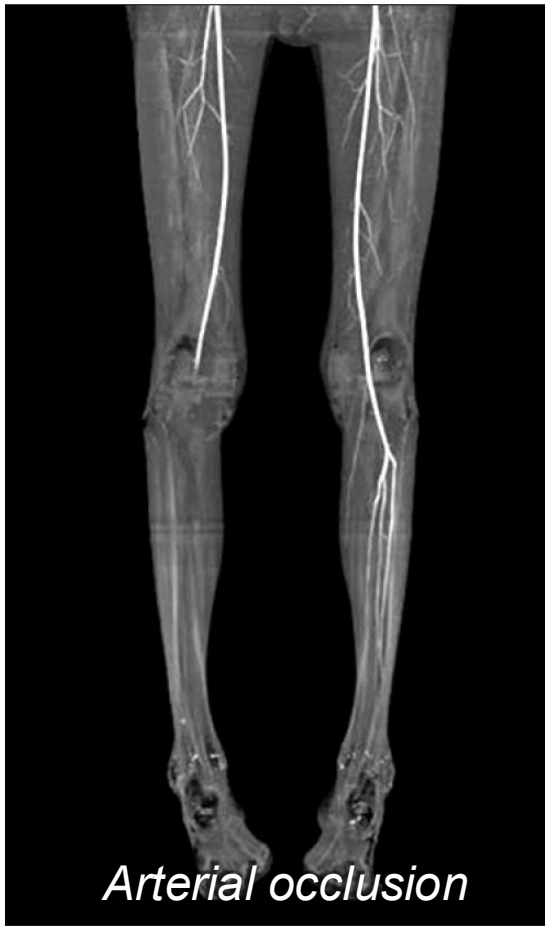


Shah, Circulation 1990; 81: 10x81

Eosinophil-mediated endothelial toxicity in humans







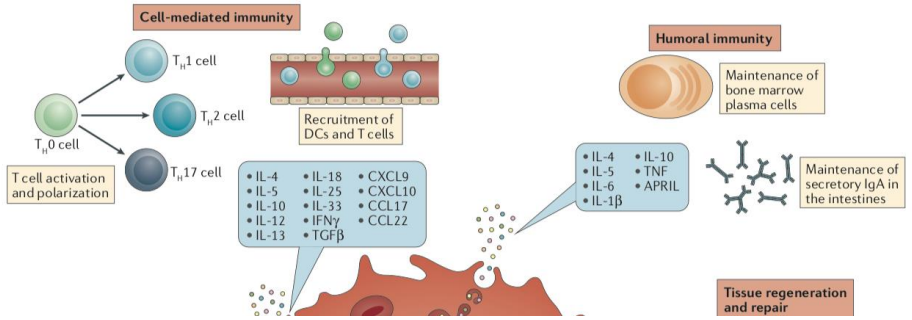
European Reference Network
for rare or low prevalence complex diseases
Network Hematological Diseases (ERN EuroBloodNet)

EHA EUROPEAN HEMATOLOGY ASSOCIATION

Webinars
EuroBloodNet

Eosinophils : Roles in Health and Disease

T cell activation and polarisation



Plasma cell survival

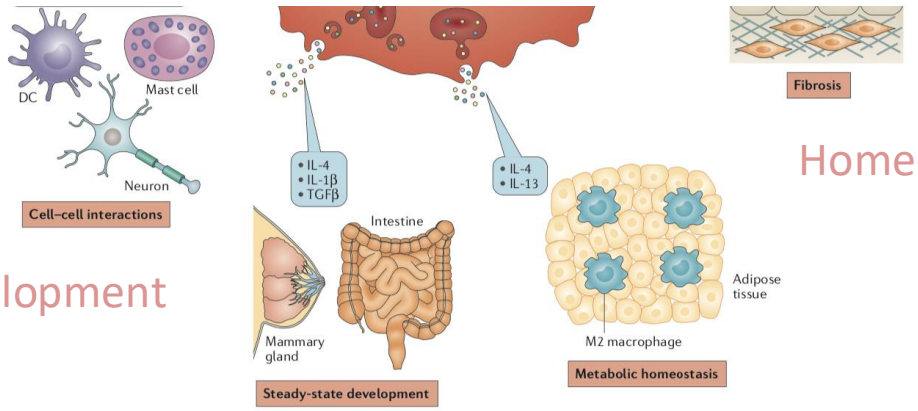
Cytotoxicity

Most data is derived from studies conducted in MICE !!

Remodelling

Fibrosis

Impact on numerous immune and non-immune cell types



Homeostasis

Development

European Reference Network for rare or low prevalence complex diseases

Network Hematological Diseases (ERN EuroBloodNet)

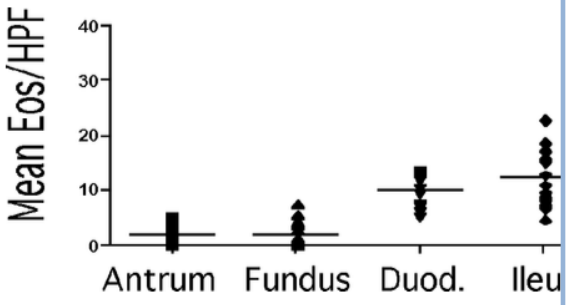
EHA EUROPEAN HEMATOLOGY ASSOCIATION

Webinars EuroBloodNet

Weller and Spencer. Nat Rev Immunol 2017; 17: 746-60.

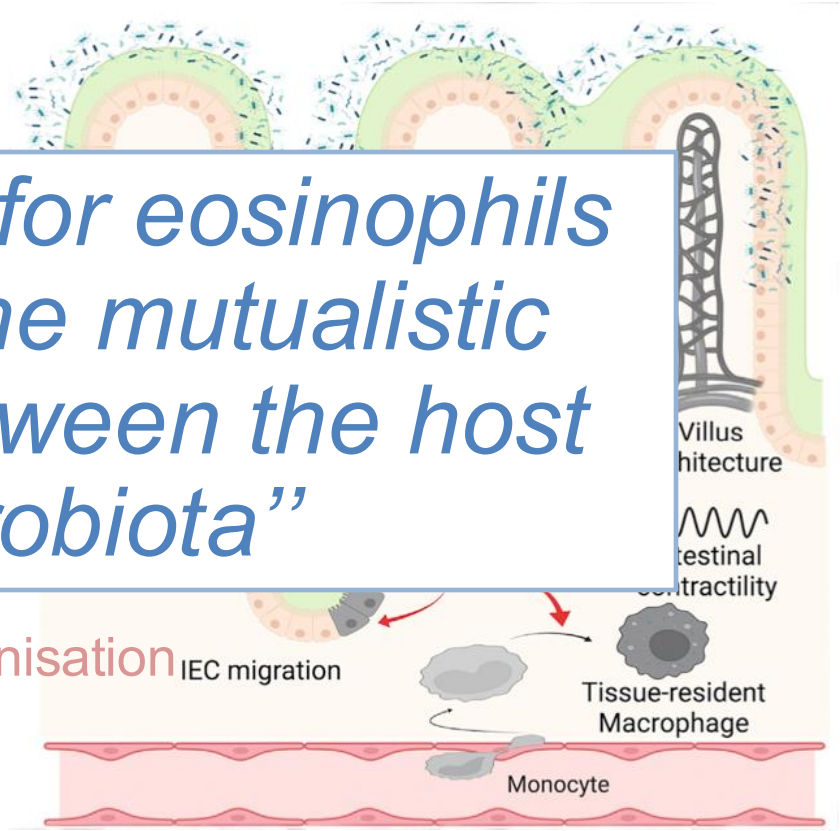
Eosinophils in the healthy gastrointestinal tract

GI eosinophils in children



Inter-cryptic

Role of GI eosinophils in new-born mice



" … critical role for eosinophils in facilitating the mutualistic interactions between the host and microbiota"

Post-natal microbial colonisation

European Reference Network for rare or low prevalence complex diseases

Network Hematological Diseases (ERN EuroBloodNet)

EHA EUROPEAN HEMATOLOGY ASSOCIATION

Webinars EuroBloodNet

DeBrosse et al, Pediatric Developmental Pathology 2006; 9:210. Ignacio et al, 2022, Immunity 55, 1250.

Definition of Hypereosinophilia

Hypereosinophilia: Blood, Counts x 10^9/L Blood	
Hypereosinophilia	>1.5 recorded on ≥2 determinations with a minimum time interval of 2 weeks
Eosinophilia	0.5 - 1.5
Normal	0.05 – 0.5 (1% - 6% WBC)
Hypereosinophilia: Tissue	
The percentage of eosinophils >20% of all nucleated bone marrow cells AND/OR	
Pathologist is of the opinion that tissue eosinophil infiltration is excessive compared with the normal physiological range, compared with other inflammatory cells or both AND/OR	
A specific eosinophil granule protein stain demonstrates extensive extracellular deposition indicative of local eosinophil activation and degranulation even in the absence of local eosinophil infiltration	

European Reference Network for rare or low prevalence complex diseases
Network Hematological Diseases (ERN EuroBloodNet)

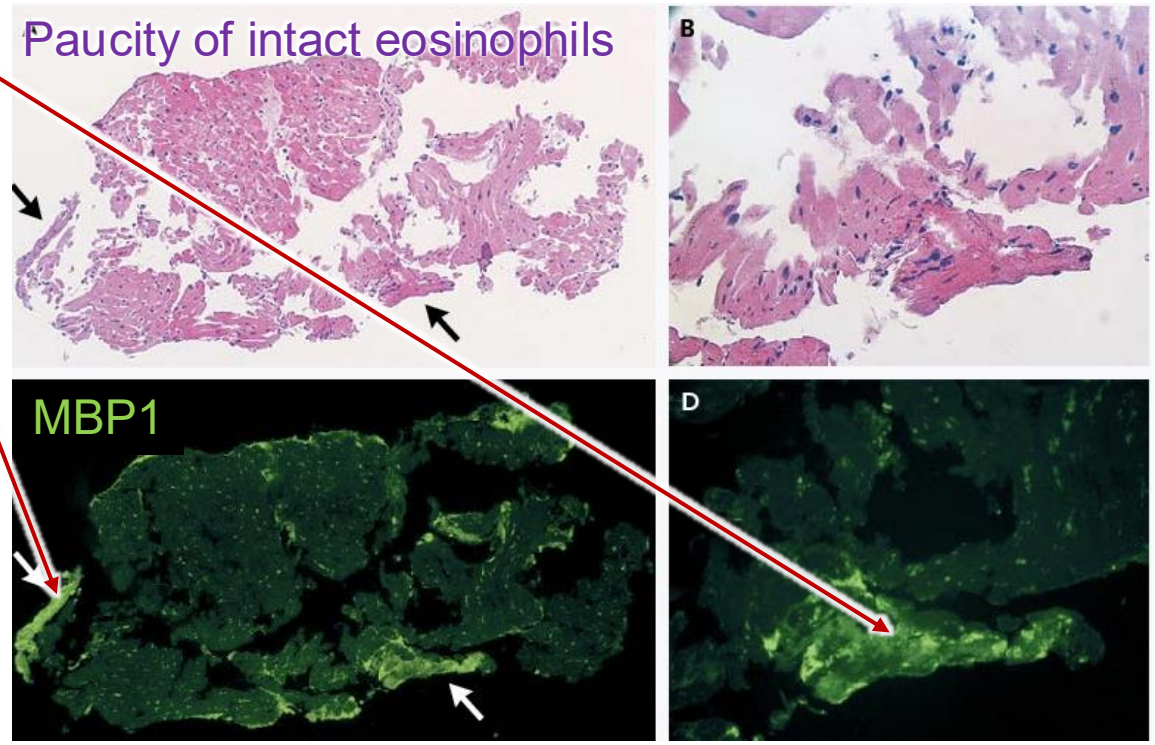
EHA EUROPEAN HEMATOLOGY ASSOCIATION

Webinars EuroBloodNet

Adapted from Valent et al. Allergy 2023 Jan;78(1):47-59

Extracellular deposition of granule proteins

A specific eosinophil granule protein stain demonstrates extensive extracellular deposition indicative of local eosinophil activation and degranulation even in the absence of local eosinophil infiltration



European Reference Network for rare or low prevalence complex diseases

Network Hematological Diseases (ERN EuroBloodNet)

EHA EUROPEAN HEMATOLOGY ASSOCIATION

Webinars EuroBloodNet

Wright et al. New Engl J Med 2011; 365:2.

Most common causes of Hypereosinophilia

- Allergic disorders
  - Atopy: ! Rarely causes HYPEReosinophilia (e.g. severe eosinophilic asthma)
  - Adverse drug reactions (e.g. DRESS)
- Parasitic infections
  - Helminthiasis mostly (e.g. Strongyloidiasis, Toxocarosis)
  - Ectoparasites (e.g. Scabies, Myiasis)
- Neoplasms - Cancer
  - Hematological malignancies (eosinophilia may be clonal or paraneoplastic)
  - Solid tumors (e.g. adenoC)

Drugs most commonly responsible for Hypereosinophilia

Antibiotics: penicillins, cephalosporins, cyclins (mainly minocycline), sulfonamides, nitrofurantoin, isoniazid, rifampicin, vancomycin.

Non-steroidal anti-inflammatory drugs

Uric acid-lowering agents: allopurinol.

Antiepileptic drugs: phenytoin, carbamazepine, phenobarbital, lamotrigine, gabapentin, valproic acid.

Sulfonamides: dapsone, sulfasalazine, antibacterial and antidiabetic sulfonamides.

Antivirals: abacavir, nevirapine, efavirenz.

Anticoagulants: heparin, fluindione.

Cancer immunotherapy: ipilimumab, nivolumab, pembrolizumab, IL-2, etc.

Miscellaneous: dupilumab, synthetic antithyroid drugs, thalidomide, diltiazem, dialysis membranes, iodinated contrast agents, phytotherapy.

Orphanet J Rare Dis. 2023 Apr 30;18(1):100.

Diverse etiologies of (hyper)eosinophilia

Category	Examples (not inclusive)
Allergic disorders*	Asthma, atopic dermatitis
Drug hypersensitivity	Varied†
Infection	
Helminthic	Varied, including strongyloidiasis, t… filariasis, schistosomiasis…
Ectoparasite	Scabies, myiasis
Protozoan	Isosporiasis…
Fungal	Coccid… …onchopulmonary …plasmosis
Viral	
Neoplasms	…ma, lymphoma, adenocarcinoma
Immunolog…	
Im…	DOCK8 deficiency, Hyper-IgE syndrome, Omenn's syndrome
…e and idiopathic	Sarcoidosis, inflammatory bowel disease, IgG4 disease, and other connective tissue disorders
Miscellaneous	Radiation exposure, cholesterol emboli, hypoadrenalism, IL-2 therapy
Rare eosinophilic disorders	Idiopathic hypereosinophilic syndrome, eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss syndrome), eosinophilic gastrointestinal disorders

'Wheezes, worms and weird diseases'

Klion AD. Blood 2015;126:1069–1077.

Definition of Hypereosinophilic Syndrome

Hypereosinophilia: Blood, Counts x 10^9/L Blood	
Hypereosinophilia	>1.5 recorded on ≥2 determinations with a minimum time interval of 2 weeks
Eosinophilia	0.5 - 1.5
Normal	0.05 – 0.5 (1% - 6% WBC)

Hypereosinophilia: Tissue
The percentage of eosinophils >20% of all nucleated bone marrow cells AND/OR
Pathologist is of the opinion that tissue eosinophil infiltration is excessive compared with the normal physiological range, compared with other inflammatory cells or both AND/OR
A specific eosinophil granule protein stain demonstrates extensive extracellular deposition indicative of local eosinophil activation and degranulation even in the absence of local eosinophil infiltration

Hypereosinophilic syndrome(s)
Criteria for blood and tissue HE fulfilled AND
Organ damage and/or dysfunction attributable to tissue HE AND
Exclusion of other disorders or conditions as main reason for organ damage

for rare or low prevalence complex diseases

Network Hematological Diseases (ERN EuroBloodNet)

EHA EUROPEAN HEMATOLOGY ASSOCIATION

Webinars EuroBloodNet

Adapted from Valent et al. Allergy 2023 Jan;78(1):47-59

End-organ damage and clinical manifestations in HES

Neurological
embolic stroke, encephalitis, peripheral neuropathy

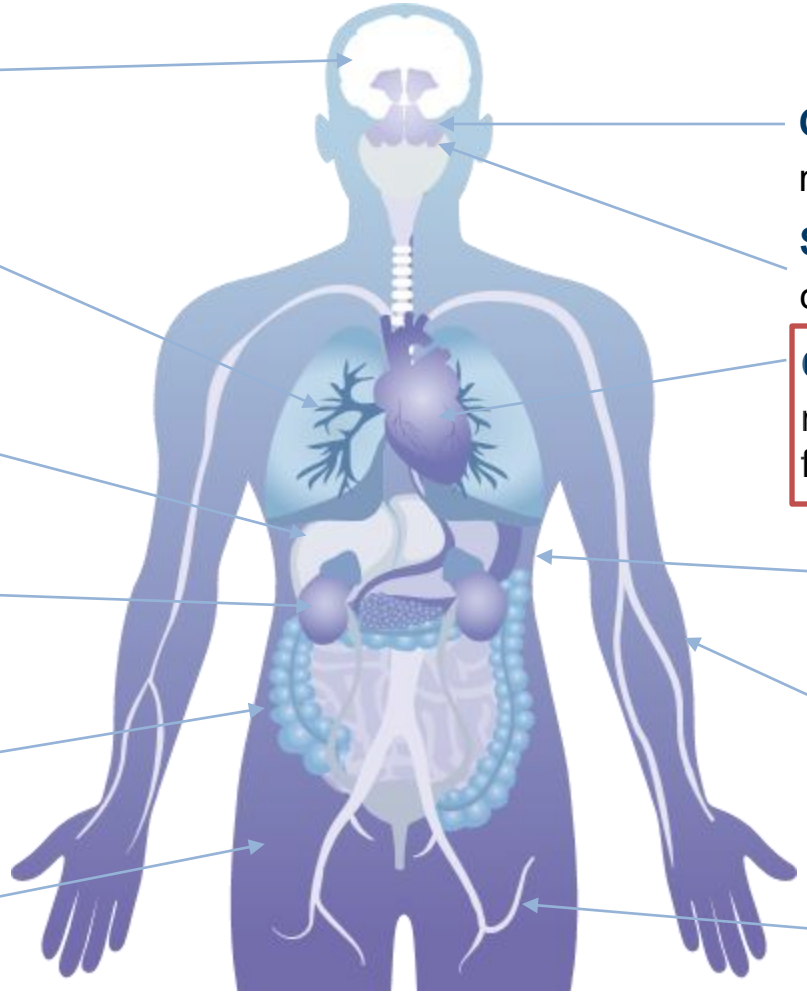
Pulmonary
asthma, eos. lung infiltrates, fibrosis, PAH vascular cuffing, pulmonary embolism

Hepatic
hepatitis, cholangitis

Renal/Urinary
interstitial nephritis, glomerulopathy, thrombotic microangiopathy, cystitis

Gastrointestinal
(gastro-)enteritis, colitis

Soft tissue / Rheumatological
angioedema, fasciitis, myositis, synovitis, arthritis



General
fatigue, myalgia, weight loss, fever

Ocular
retinal micro-emboli, choroidal inflammation

Sino-nasal cavities
chronic rhino-sinusitis, polyposis

Cardiac
myocarditis, intracavitary thrombus, subendocardial fibrosis, valve entrapment, pericarditis

Hematological
splenomegaly, lymphadenopathy

Dermatologic
pruritis, eczema, dermatitis, urticaria, erythroderma, bullous lesions

Vascular
art/ven thrombosis, microvascular damage, Raynaud's, digital necrosis, aneurysms, arterial dissection, vasculitis

European Reference Network
for rare or low prevalence complex diseases
Network Hematological Diseases (ERN EuroBloodNet)

EHA EUROPEAN HEMATOLOGY ASSOCIATION

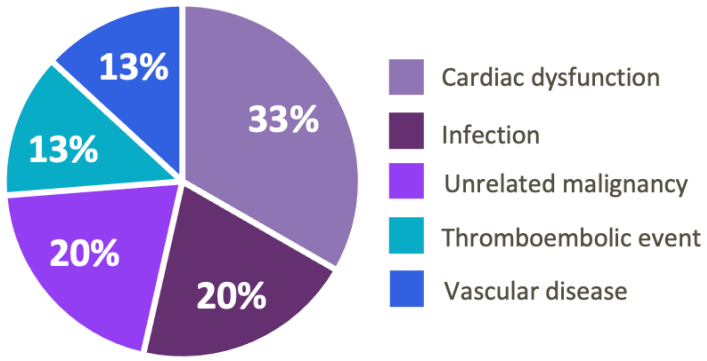
Webinars
EuroBloodNet

Cogan & Roufosse. Expert Rev Hematol 2012;5:275. Roufosse F et al. UpToDate.

Cardiovascular morbidity-mortality in HES

Cause of death in 15 patients among those diagnosed with HES (N=247)

- Cardiovascular complications are a significant cause of morbidity in HES patients
- They also account for a significant proportion of deaths



A retrospective review of morbidities and causes of death in HES patients at the Mayo Clinic over 19 years

Complications include :

- Congestive heart failure
- Restrictive cardiomyopathy due to subendocardial fibrosis
- Valve regurgitation
- Intracardiac thrombus formation
- Myocardial ischaemia
- Arrhythmia
- Pericarditis
- Thromboembolic disease

European Reference Network for rare or low prevalence complex diseases
Network Hematological Diseases (ERN EuroBloodNet)

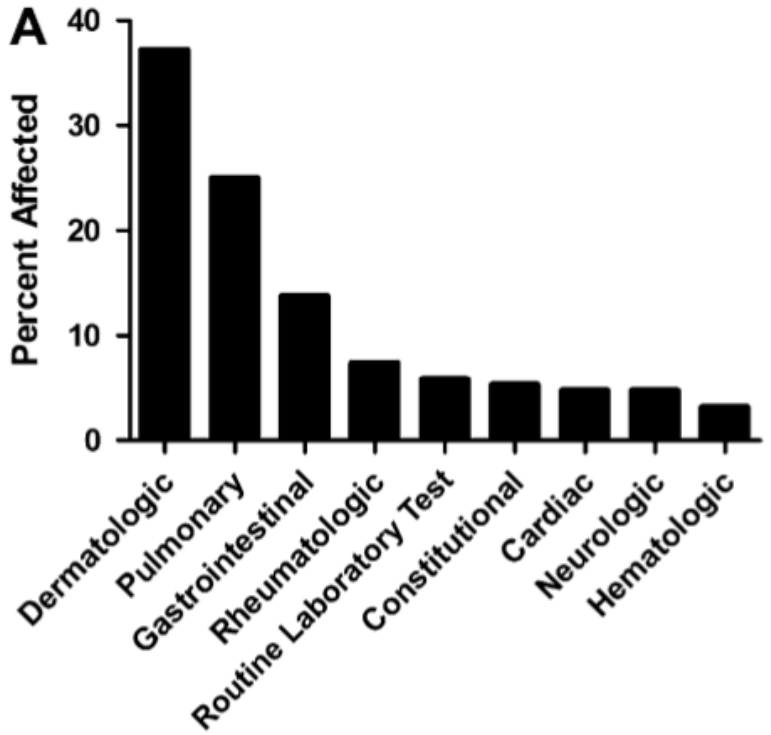
EHA EUROPEAN HEMATOLOGY ASSOCIATION

Webinars EuroBloodNet

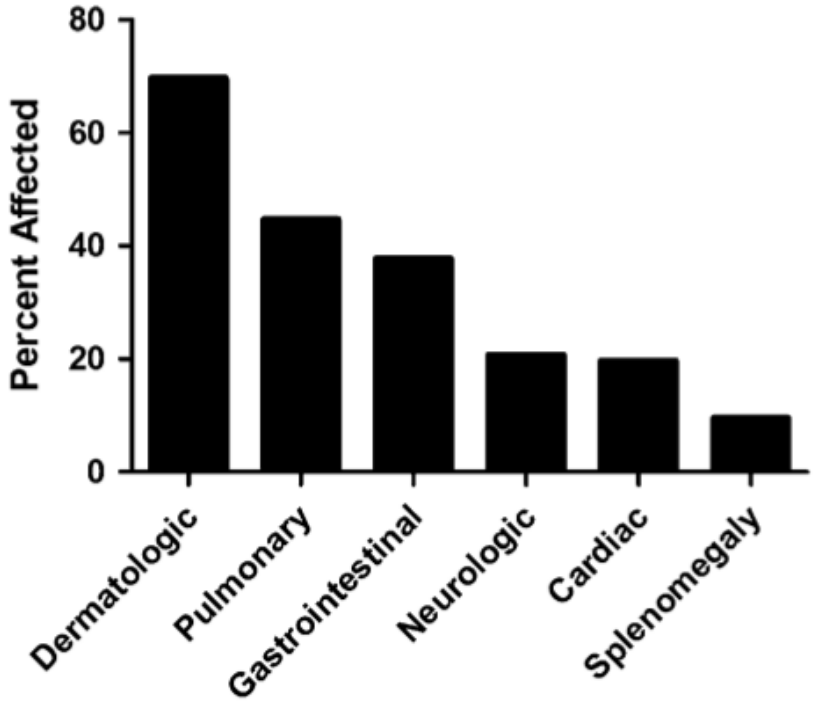
Podjasek JC & Butterfield JH. Leuk Res. 2013;37:392–395

Prevalence of end-organ damage in HES

Initial clinical presentation



Subsequent clinical manifestation



Multi-center retrospective study, 11 expert centers, 188 patients

European Reference Network
for rare or low prevalence complex diseases
Network Hematological Diseases (ERN EuroBloodNet)

EHA EUROPEAN HEMATOLOGY ASSOCIATION

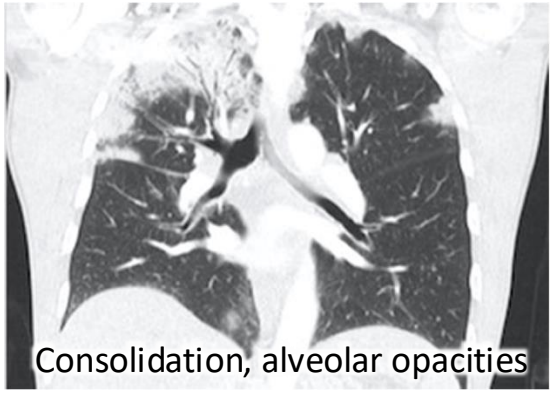
Webinars
EuroBloodNet

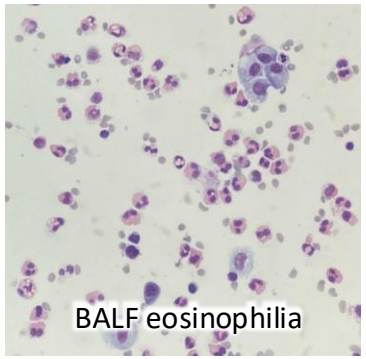
Ogbogu et al. J Allergy Clin Immunol 2009; 124:1319.

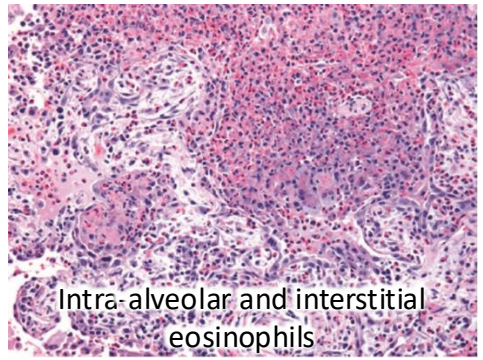
Organ-restricted HES

Hypereosinophilic syndrome(s)
Criteria for blood and tissue HE fulfilled AND
Organ damage and/or dysfunction attributable to tissue HE AND
Exclusion of other disorders or conditions as main reason for organ damage
Tissue/organ-restricted HES
Tissue HE but criteria for blood HE not fulfilled AND
Organ damage and/or dysfunction attributable to tissue HE AND
Exclusion of other disorders or conditions as major reason for organ damage

Chronic eosinophilic pneumonia


Consolidation, alveolar opacities


BALF eosinophilia


Intra-alveolar and interstitial eosinophils

European Reference Network for rare or low prevalence complex diseases
Network Hematological Diseases (ERN EuroBloodNet)

EHA EUROPEAN HEMATOLOGY ASSOCIATION

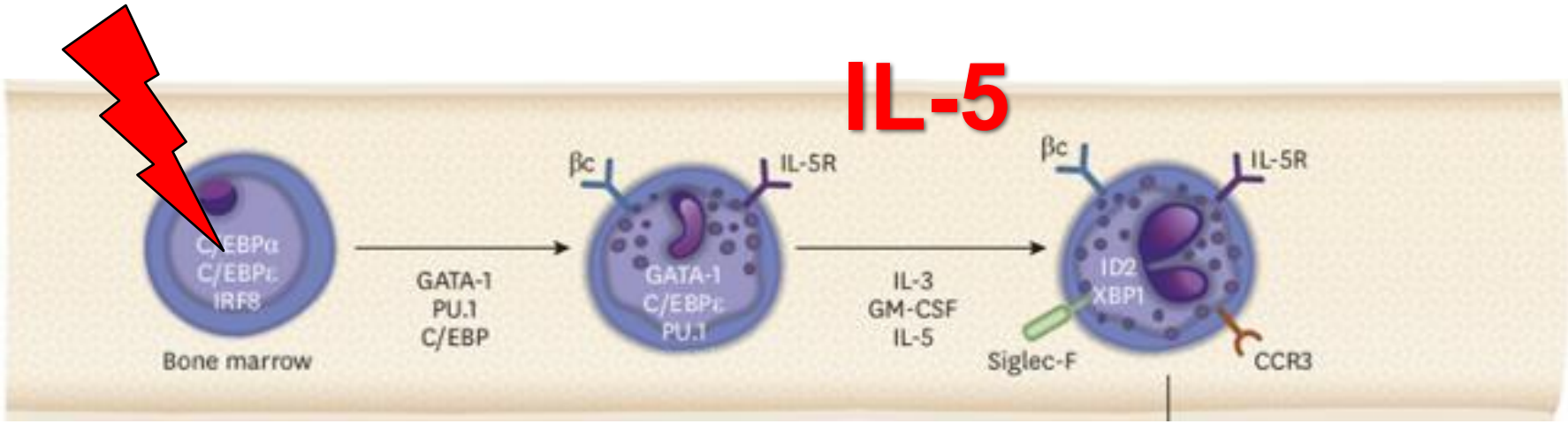
Webinars EuroBloodNet

Crowe et al. Therapeutics and Clinical Risk Management 2019;15: 397. Suzuki et al. Allergology International 2019; 68: 413.

Pathogenesis of hypereosinophilia in HES

Somatic mutation driving clonal eosinophil expansion

Increased presence of eosinophilopoietic factors driving polyclonal eosinophil expansion



Familial hypereosinophilia: mapped to cytokine gene cluster 5q31-q33

UNKNOWN

European Reference Network for rare or low prevalence complex diseases

Network Hematological Diseases (ERN EuroBloodNet)

EHA EUROPEAN HEMATOLOGY ASSOCIATION

Webinars EuroBloodNet

Pathogenic variants of HES

Myeloid variant HES

FIP1L1-PDGFRA

Other cytogenetic rearr (PDGFRA/B, FGFR1, …)

Chronic eosinophilic leukemia

Constellation of myeloproliferative features

Idiopathic HES (~70%)

Lymphoid variant HES

Clonal CD3-CD4+ T cells

Other phenotypic abN (CD3+TCRα/β+CD4-CD8-, CD3+CD4+CD7- …)

Constellation of type 2 inflammation markers

Clinical variants of HES

Multi-organ (systemic) disease

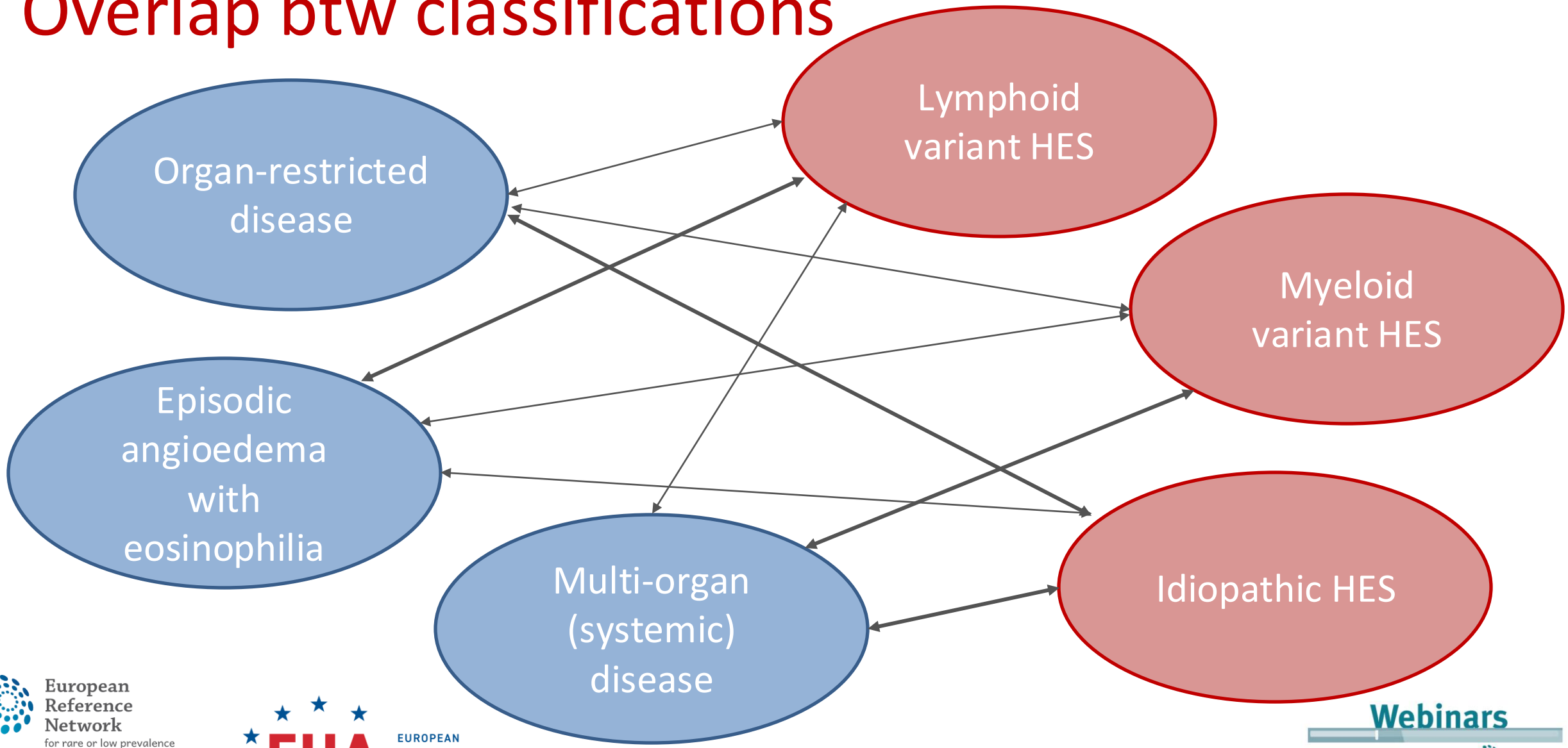
Gleich's syndrome
Angioedema, fever
High IgM

Episodic angioedema with eosinophilia

Organ-restricted disease

Chronic eosinophilic pneumonia
Eosinophilic dermatitis
Eosinophilic gastroenteritis …

Overlap btw classifications



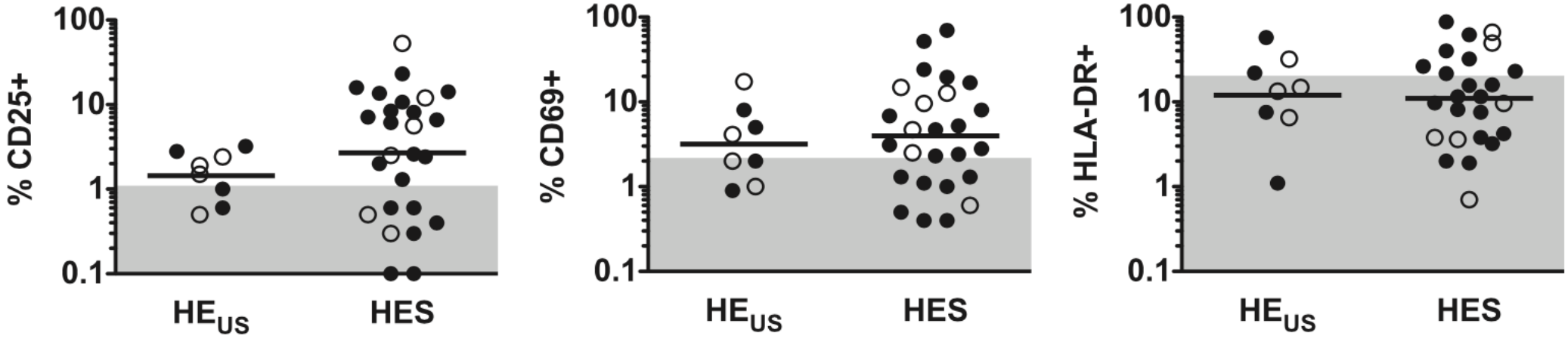
Hypereosinophilia of Undetermined Significance

- Unexplained hypereosinophilia
- Persisting for 5 years or more
- In the absence of clinical complications

Recommendations

- Follow-up for eos-mediated complications
- No treatment

No observed difference in surface expression of eosinophil activation markers



European Reference Network
for rare or low prevalence complex diseases
Network Hematological Diseases (ERN EuroBloodNet)

EHA EUROPEAN HEMATOLOGY ASSOCIATION

Webinars
EuroBloodNet

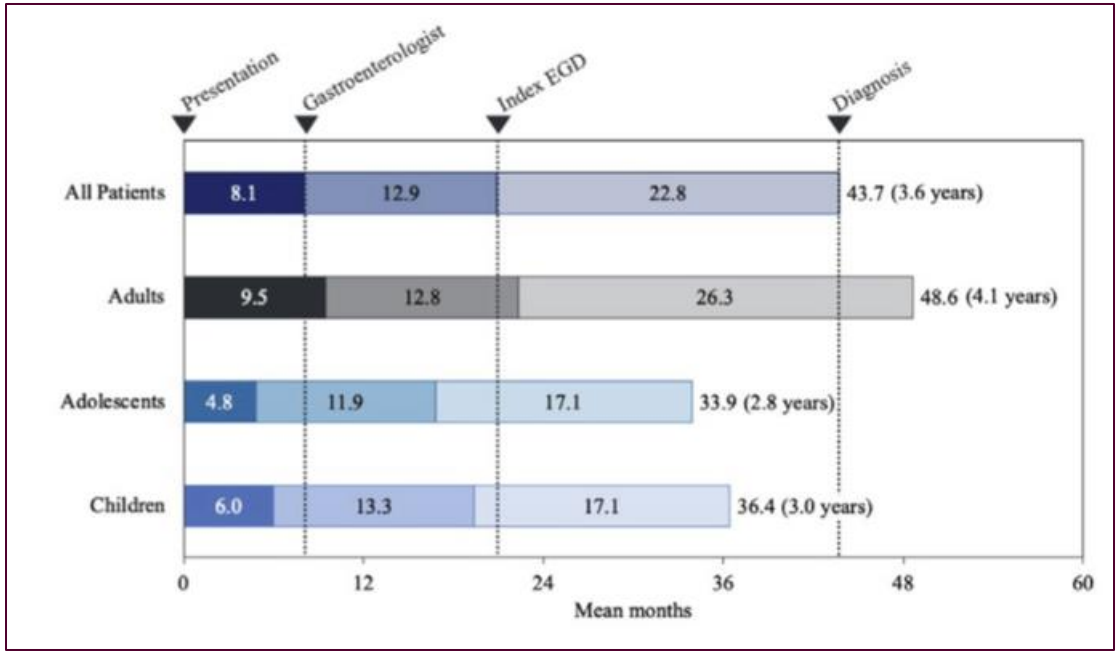
Chen et al. J Allergy Clin Immunol 2014;133(4):1195.

Delayed diagnosis of complex eosinophilic conditions

Rare diseases:
average delay 5 years

- Eosinophilic esophagitis: 4 yrs (adults)
- Eosinophilic gastritis/duodenitis: 3.6 yrs
- Lymphocytic HES: 3.5 yrs
- Eosinophilic fasciitis: 8-12 months

Eosinophilic Gastritis and/or Duodenitis



European Reference Network
for rare or low prevalence complex diseases
Network Hematological Diseases (ERN EuroBloodNet)

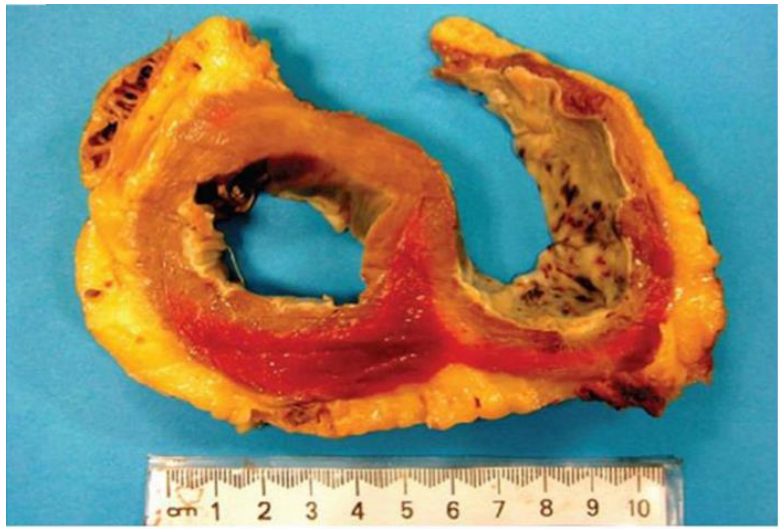
EHA EUROPEAN HEMATOLOGY ASSOCIATION

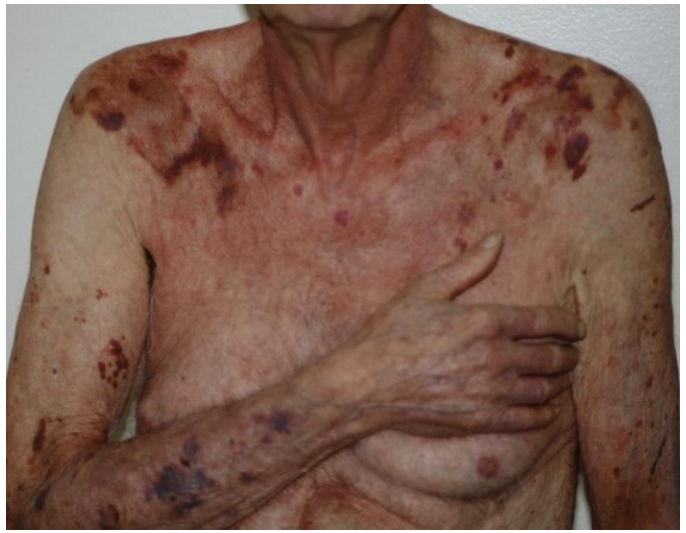
Webinars
EuroBloodNet

Cottet et al. Med Sci (Paris). 2018;43. Chehade et al. J Allergy Clin Immunol Pract. 2021;S2213-2198:00044-1. Carpentier et al. Front Immunol 2020; 11:1765.

Consequences of Diagnostic Delay

- Prolonged disease activity → accumulation of irreversible damage → disease-related morbidity / death
- Empirical use of non-targeted therapy → typically systemic CS → treatment-related morbidity
- Anxiety, depression, rejection, social and professional withdrawal





Take home messages

1. Eosinophils have a propensity to home to tissues where, if activated, they can cause damage through release of granule proteins, Charcot Leyden crystals, and extracellular traps.
2. In healthy mice, eosinophils can be found at sites of enhanced cellular turnover, where they regulate local immunity and contribute to repair and remodelling. Homeostatic roles in humans remain largely unknown.
3. Hypereosinophilia (HE) can be due to uncontrolled clonal expansion in presence of an acquired mutation in a hematopoietic stem cell, or polyclonal expansion secondary to the increased production of eosinophilopoietic factors, namely IL-5.
4. Persistent tissue HE may lead to organ damage; practically no organs are spared, but cardiovascular complications are those associated with the most morbidity and mortality.
5. Hypereosinophilic conditions are numerous; while some are common (e.g. severe asthma), others are rare diseases (e.g. hypereosinophilic syndrome)(HES).
6. HES is a systemic hypereosinophilic condition characterized by persistent blood and tissue HE associated with eosinophil-mediated organ damage and/or dysfunction.
7. This rare disease must be diagnosed and treated early to prevent irreversible damage.

SO JOIN US TO LEARN MORE!

May 13th
May 20th
June 3rd

THANK YOU FOR YOUR ATTENTION

H.U.B
Hôpital Erasme ULB
BXL
INSTITUT JULES BORDET INSTITUUT
ULB
Hôpital Universitaire des Enfants Reine Fabiola
Universitair Kinderziekenhuis Koningin Fabiola
fnrs
LA LIBERTÉ DE CHERCHER
International Eosinophil Society
IES
European Reference Network
for rare or low prevalence complex diseases
Network Hematological Diseases (ERN EuroBloodNet)
EHA
EUROPEAN HEMATOLOGY ASSOCIATION
EuroBloodNet
Webinars
EuroBloodNet