Biologics in Paediatric Severe Asthma Management

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LSBU NMP Update Session – 21/07/2023

Session Objectives

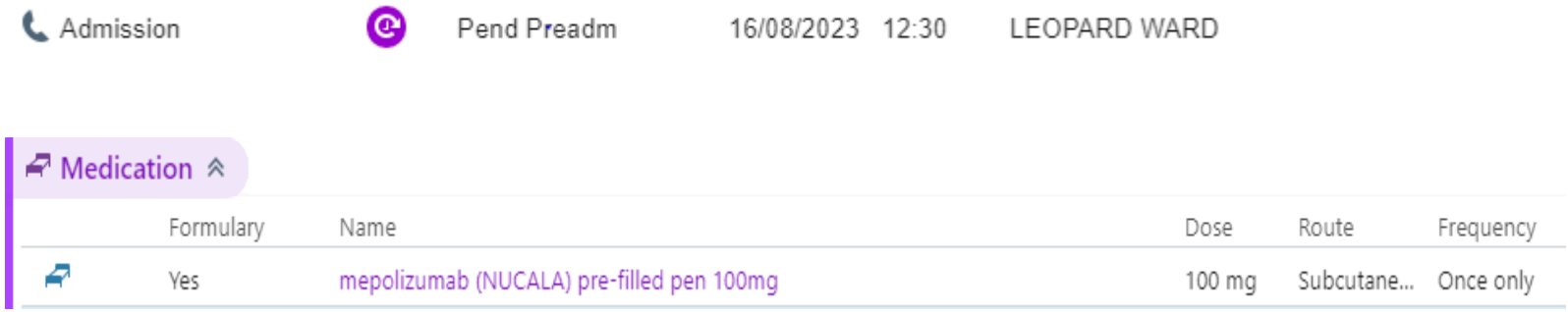
- Overview of the Complex Asthma Service
- The ACP role in supporting the prescription and administration of Biologics
- Review evidence and rational for biologics in paediatric severe therapy resistant asthma.
- Focusing on:
  - Assessment for Biologic eligibility
  - Characterising airway inflammation
  - Future directions

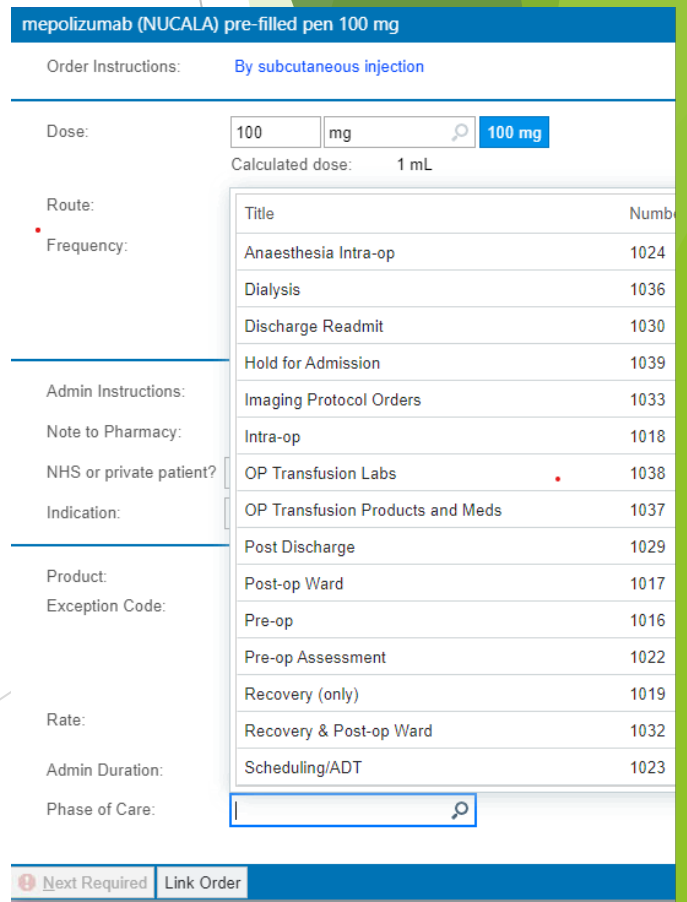
GOSH and the Complex Asthma Service

- NHS England-funded service to provide tertiary level asthma care to patients referred from local asthma/respiratory services
- The service has:
  - 2 Consultants; both have other clinical duties but have dedicated PA Time for the Asthma Role
  - Full time Band 7 CNS
  - Outpatient clinics currently run every Friday morning
  - The service is also supported by:
    - Lung function service: for onsite and at-home lung function testing
    - Physiotherapy
    - Psychology
    - Advanced Clinical Practitioner Team

Role of the ACP team

- Team was set up in 2019 to support the respiratory patient cohort
- Lead and support on the review of patients attending for biologic therapy
- Patient assessment to ensure suitability for therapy
  - Management of any acute issues alongside supporting patients and families
- Medication prescribing via EPIC
  - This is done in advance of the patient attending the appointment so that the therapy is available on the ward to reduce time scale for all those involved





Severe/complex asthma

- Poorly controlled symptoms and/or frequent/severe exacerbations despite high-dose treatment

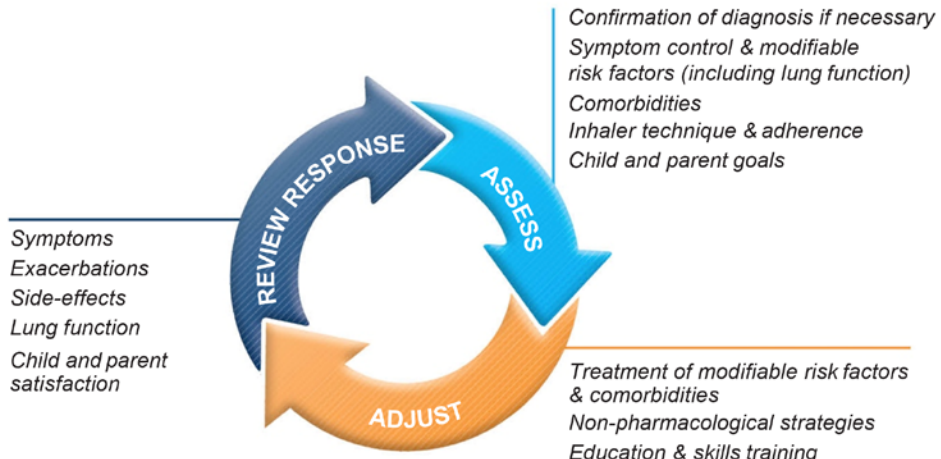
- Prevalence: 2-3% of children with asthma[1,2]
  - High vulnerability – risk of attacks
  - Risk of low lung function trajectories
  - High treatment burden and risk of adverse medication effects
  - High health care utilisation

- Requires comprehensive Multi-Disciplinary Team evaluation

Box 3-5B

Children 6-11 years

Personalized asthma management:
Assess, Adjust, Review response



Confirmation of diagnosis if necessary
Symptom control & modifiable risk factors (including lung function)
Comorbidities
Inhaler technique & adherence
Child and parent goals

Symptoms
Exacerbations
Side-effects
Lung function
Child and parent satisfaction

Treatment of modifiable risk factors & comorbidities
Non-pharmacological strategies
Education & skills training
Asthma medications

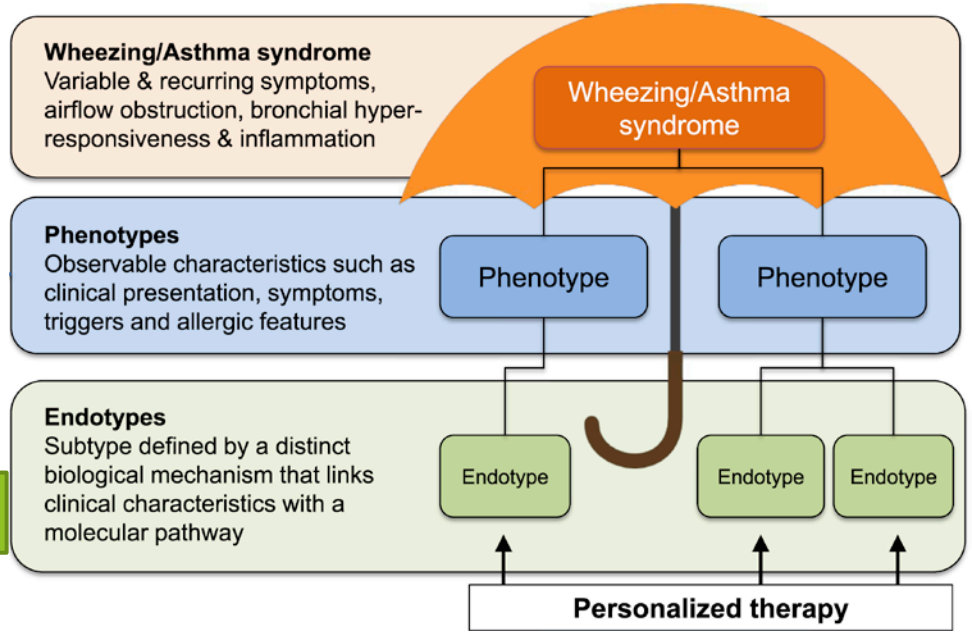
Asthma medication options:
Adjust treatment up and down for individual child's needs

	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
PREFERRED CONTROLLER to prevent exacerbations and control symptoms		Daily low dose inhaled corticosteroid (ICS) (see table of ICS dose ranges for children)	Low dose ICS-LABA, or medium dose ICS	Medium dose ICS-LABA Refer for expert advice	Refer for phenotypic assessment ± add-on therapy, e.g. anti-IgE
Other controller options	*Low dose ICS taken whenever SABA taken*; or daily low dose ICS*	*Leukotriene receptor antagonist (LTRA), or low dose ICS taken whenever SABA taken**	*Low dose ICS+LTRA*	*High dose ICS-LABA, or add-on tiotropium, or add-on LTRA*	*Add-on anti-IL5, or add-on low dose OCS, but consider side-effects*
RELIEVER	*As-needed short-acting β_2 -agonist (SABA)*				

* Off-label; separate ICS and SABA inhalers; only one study in children

Evaluation of severe therapy-resistant asthma

- Is airway inflammation present?
  - If so what is the inflammatory endotype? eosinophilic; neutrophilic; mixed; paucigranulocitic?
- Is the airway inflammation steroid-responsive?
  - Is there T helper 2 (T_h2)-mediated eosinophilic inflammation?
- What is the relationship between symptoms and degree of inflammation?
- Is there evidence of persistent airflow limitation?



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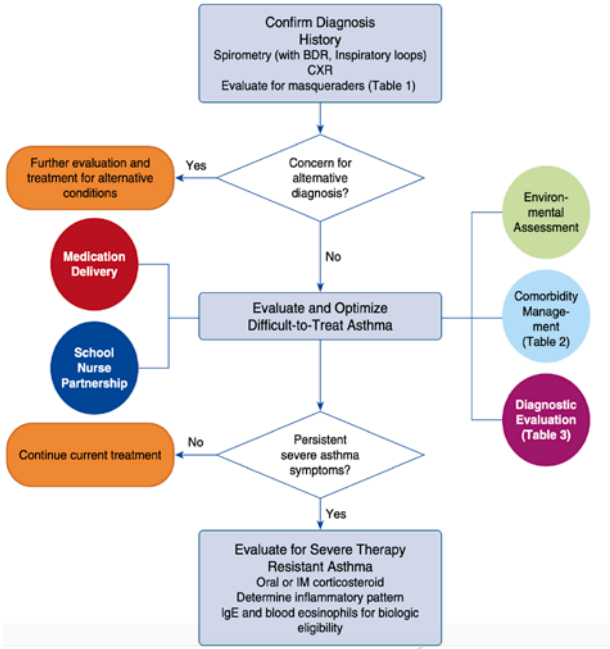

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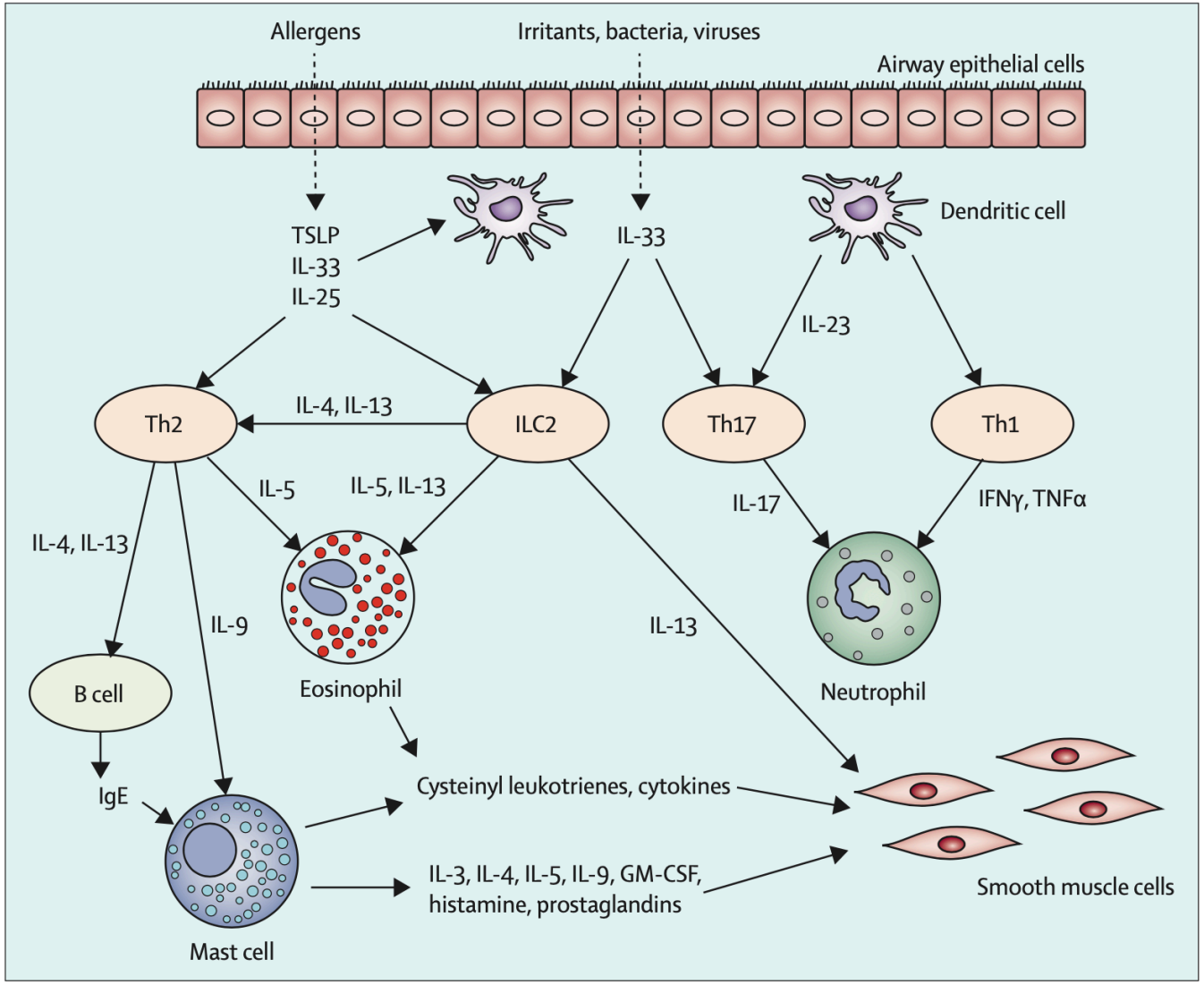
T_h2 and T_h1 inflammatory pathways

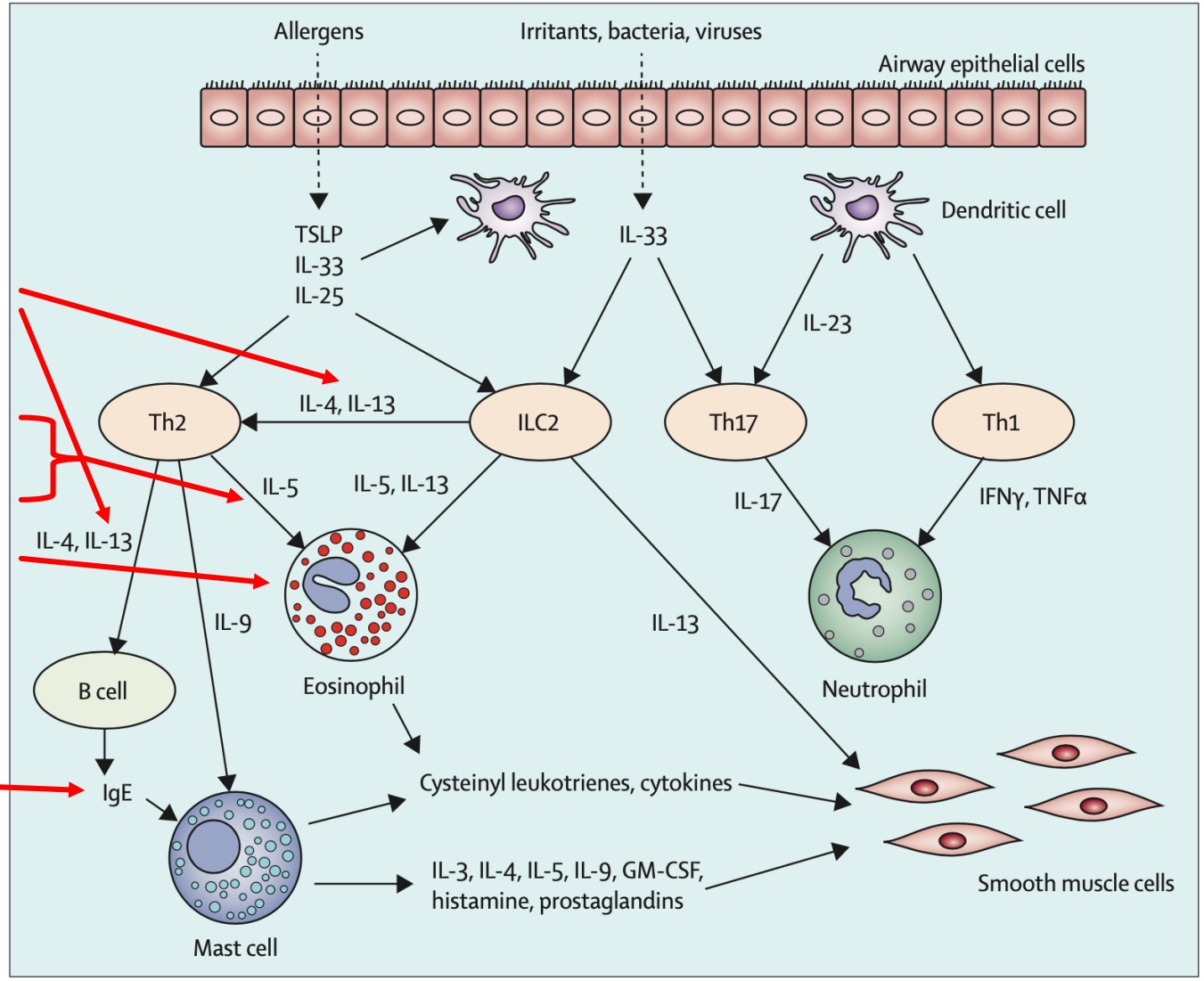


T_h2 and T_h1 inflammatory pathways

Dupilumab

Mepolizumab
Reslizumab
Benralizumab

Omalizumab



Biologic therapies for severe therapy-resistant asthma

- Anti IgE
  - Omalizumab
- Drugs targeting IL-5
  - Mepolizumab
  - Reslizumab
  - Benralizumab
- Drugs targeting IL-4 and IL-13
  - Dupilumab

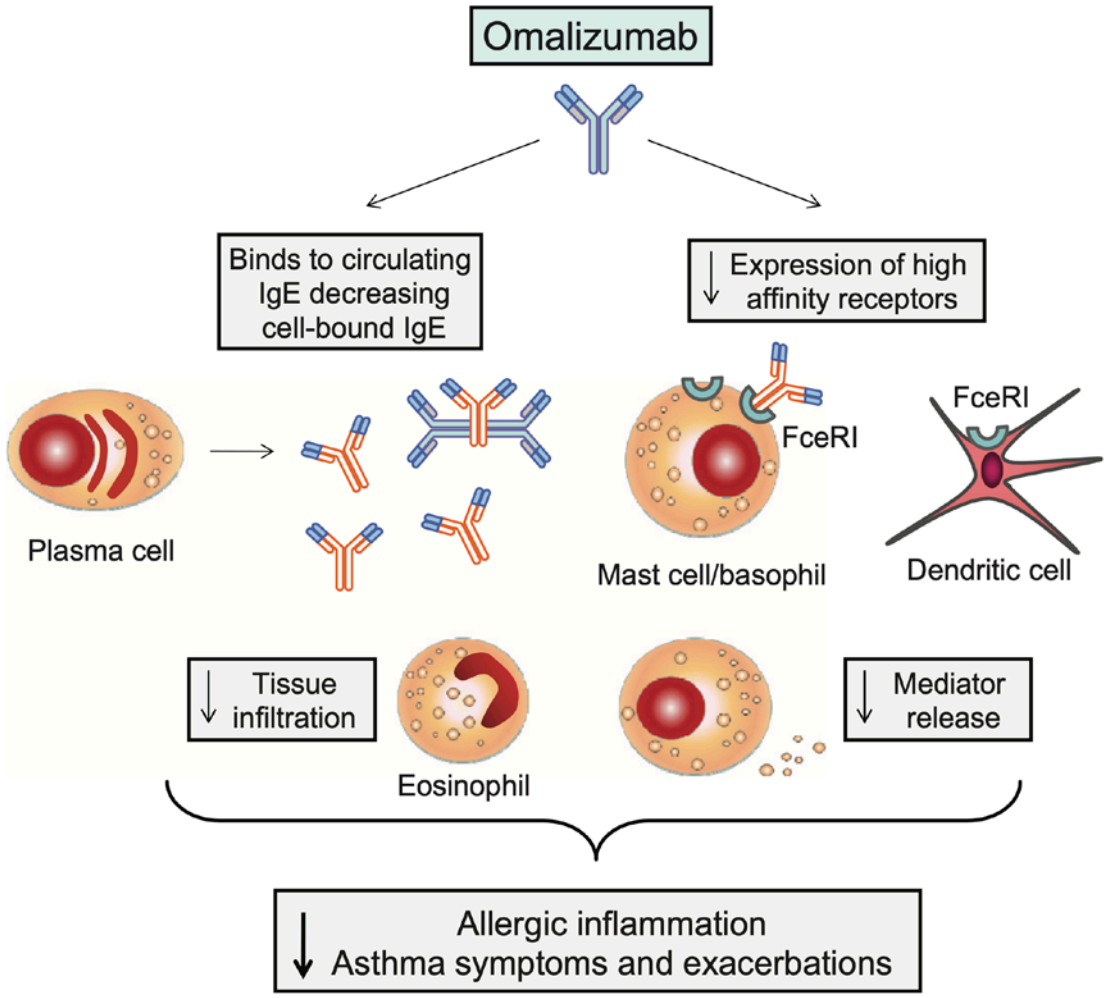
Biologic therapies for severe therapy-resistant asthma

- Anti IgE
  - Omalizumab*
- Drugs targeting IL-5
  - Mepolizumab*
  - Reslizumab
  - Benralizumab
- Drugs targeting IL-4 and IL-13
  - Dupilumab**
- Drugs targeting thymic stromal lymphopoietin (TSLP)
  - Tezepelumab

* Licensed >6 yrs
** Licensed >12 yrs

Omalizumab

- Recombinant humanised monoclonal anti-IgE antibody
- Binds to the F_c component of free IgE

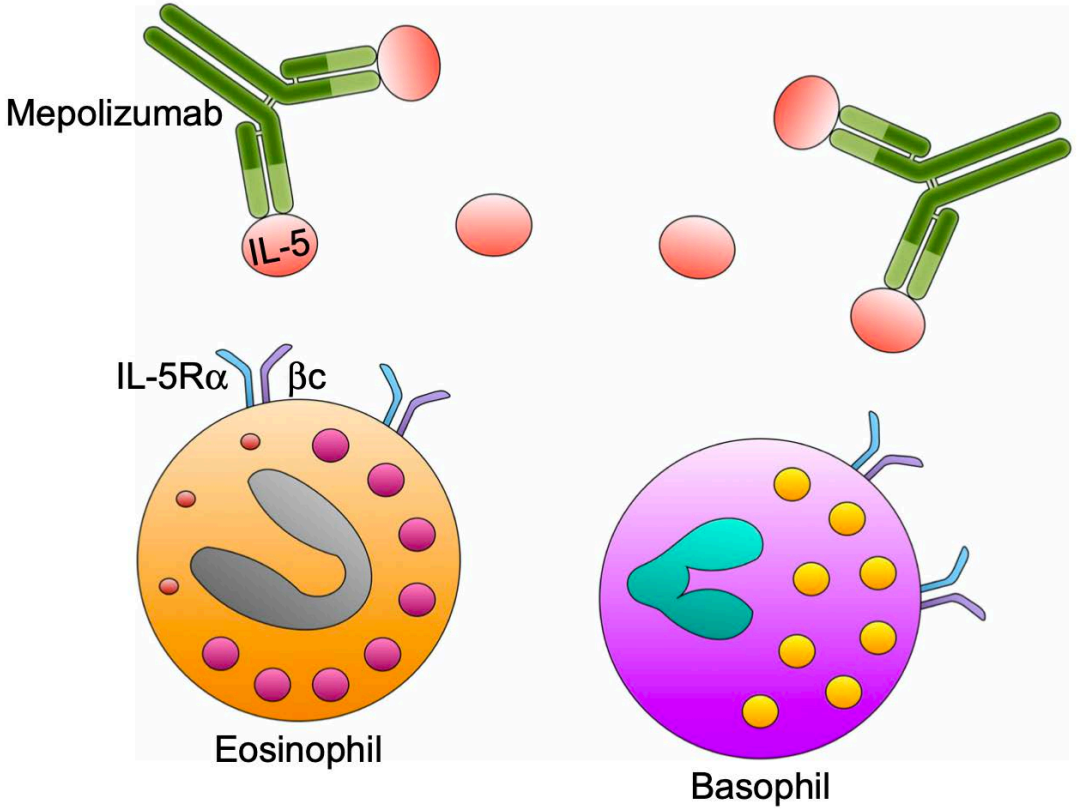


Omalizumab licensing

- Approved add-on therapy in children >6 with severe allergic asthma
  - Elevated total IgE (30-1500 IU/ml) + positive allergen-specific IgE or skin test to ≥1 aeroallergen
  - Multiple asthma attacks (≥4 courses of steroids in 12 months)
  - Optimised standard therapy
- Dosing
  - 75-600 mg sub-cut every 2-4 weeks
  - Assessment of efficacy required at 16 weeks
- Costs
  - £128 per 75mg vial
  - £1.5k – £12k per year

Mepolizumab

- Humanized monoclonal antibody to circulating IL-5
- Reduces maturation, recruitment, activation and survival of eosinophils



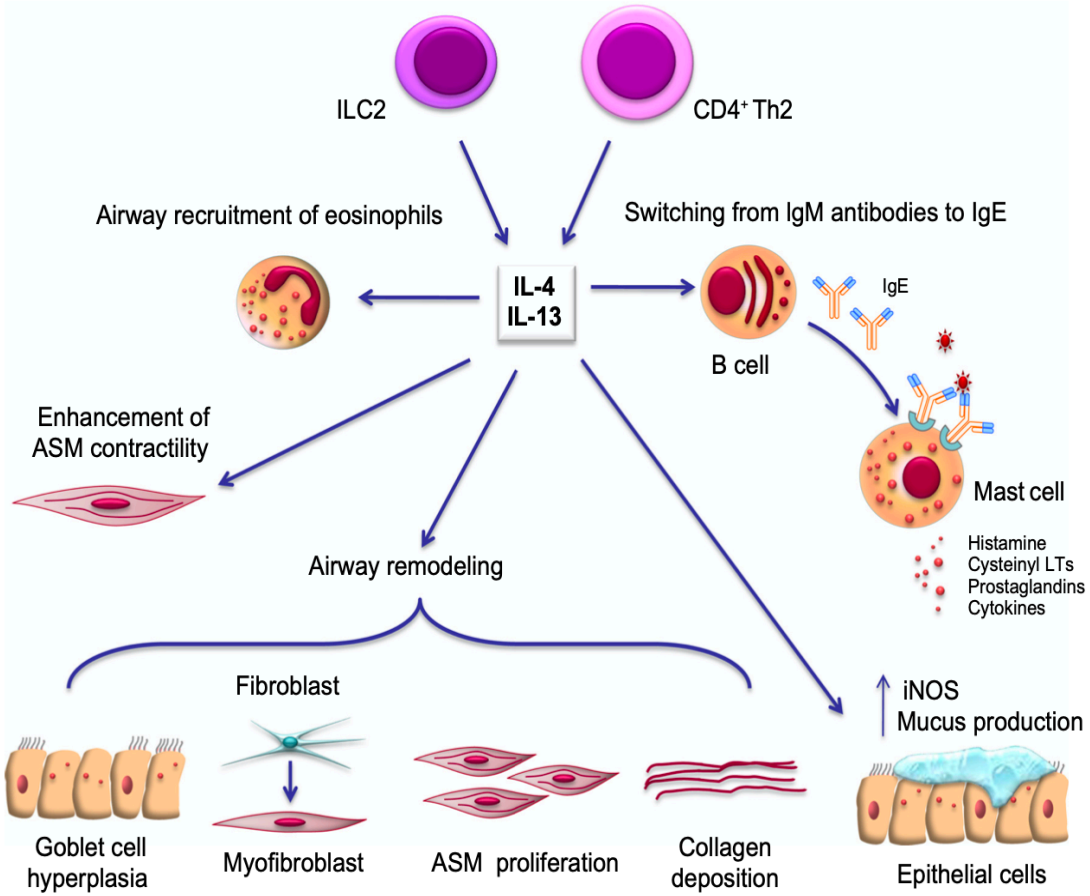
Mepolizumab licensing

- Approved add-on therapy in patients >6 with uncontrolled severe eosinophilic asthma and
  - Eosinophils ≥0.3 x 10^9/L and ≥4 attacks requiring steroids in previous year

  Or
  - Eosinophils ≥0.4 x 10^9/L and ≥3 attacks requiring steroids in previous year
  - Optimised standard therapy
- Dosing
  - 40 mg or 100 mg sub-cut every 4 weeks
  - Assessment of efficacy required at 12 months
- Costs
  - £840 per 100mg dose
  - £10k per year

Dupilumab

- Recombinant human mono-clonal antibody inhibiting IL-4 and IL-13 signalling
- Reduces multiple mediators of type 2 inflammation



Dupilumab licensing

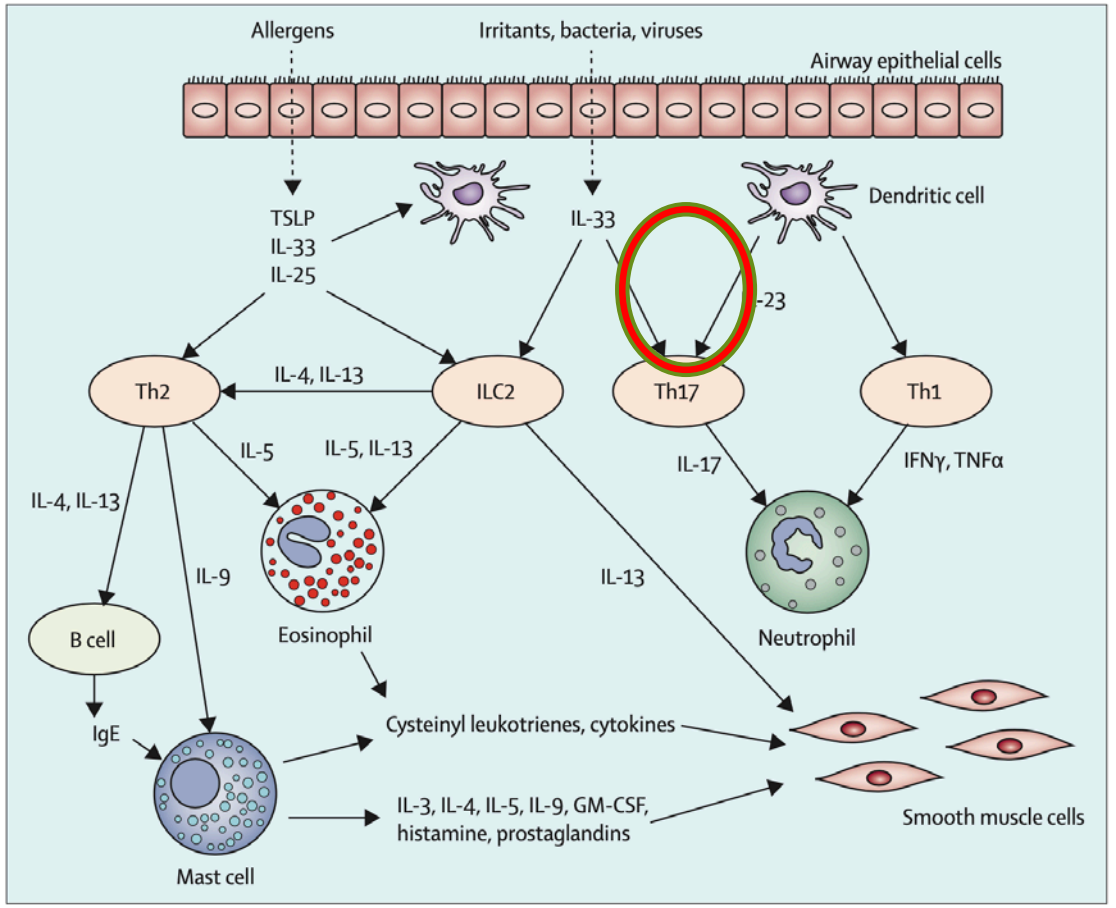
- Approved add-on therapy in patients >12 with uncontrolled severe T_h2-high asthma and
  - Eosinophils ≥0.15 x 10^9/L and FeNO ≥25 ppb in previous 12 months
  - ≥4 attacks requiring systemic steroids in previous 12 months
  - Ineligible for or has not responded adequately to mepolizumab
- Dosing
  - 400mg first dose, then 200mg every 2 weeks
  - Assessment of efficacy required at 12 months
- Costs
  - £1.2k per year

Adverse Reactions

Biologic	Common adverse reactions	Rare agent-specific adverse reactions
Omalizumab	Injection site reactions	Serum sickness, hypereosinophillic conditions (e.g. EGPA), anaphylaxis
Mepolizumab	Injection site reactions	Helminth infections, hypereosinophillic conditions (e.g. EGPA)
Dupilumab	Injection site reactions, arthralgia Upper respiratory infections/pharyngitis	Transient eosinophilia, helminth infections, conjunctivitis (with atopic dermatitis)

What's on the horizon?

- Benralizumab – anti-IL-5Ra
  - Reduced exacerbations (28%-51%) in adult (12-75yrs) studies
  - Adolescent data (n=108) inconclusive
- Tezepelumab – anti-thymic stromal lymphopoietin (TSLP)
  - T2-high and non-T2-high asthma
  - Reduced exacerbations (56%) in adult (12-80yrs) studies
  - Encouraging adolescent data
  - Paediatric study planned



Any questions?

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