Obstructive Lung Disorders
COPD & Asthma

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**Naïve T cell Differentiation**

![Diagram of T cell differentiation](image)

- **Th1**
  - **Cellular Immunity**
  - e.g. bacteria, viruses
  - **TNF-β**, **IL-12**, **IL-18**

- **Th2**
  - **Humoral Immunity**
  - e.g. parasites, allergens
  - **IL-4**, **IL-5**, **IL-13**

- **Treg**
  - **Tolerance auto-antigens**
  - e.g. cell death
  - **TGF-β**, **IL-10**

- **Th17**
  - **Autoimmune disease**
  - e.g. asthma, RA
  - **TGF-β**, **IL-6**, **IL-23**, **IL-17**

**Dendritic Cell**

**Naïve T cell**

**Effector T cell**

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**COPD Epidemic**

- Globally approx. 210 Million persons suffer from COPD
- 2005 approx. 3 Million died from COPD (=5% global causes of death)
- in Europe 200.000 – 300.000 die annually from COPD
- if no measures taken to reduce risk factors (tobacco smoking) → number of COPD-related death cases will increase by 30% in the next decade

Adapted from: World Health Organization, 2009, fact sheet Nr. 315

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Epidemiology COPD – Mortality

percent change age-corrected mortality rates, USA, 1965-1998

GOLD (Global Initiative for Chronic Obstructive Lung Disease), Workshop Report, Updated 2003.
BIC 2018

COPD Diagnosis: too little too late...

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Mechanisms of Airflow Limitation in COPD

Small Airways Disease
- Airway inflammation
- Airway fibrosis, luminal plugs
- Increased airway resistance

Parenchymal Destruction
- Loss of alveolar attachments
- Decrease of elastic recoil

AIRFLOW LIMITATION
BIC 2018

Barnes P, NEJM 2000,343:269-280
Risk Factors for COPD

- Genes
- Infections
- Socio-economic status
- Aging Populations

- Cigarette smoke
- Occupational dust and chemicals
- Environmental tobacco smoke (ETS)
- Indoor and outdoor air pollution

Healthy lung

COPD
Emphysema
Diagnosis of COPD

**SYMPTOMS**
- shortness of breath
- chronic cough
- sputum

**EXPOSURE TO RISK FACTORS**
- tobacco
- occupation
- indoor/outdoor pollution

**SPIROMETRY:** Required to establish diagnosis

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**Asthma Definition**

**Heterogenous** disorder & chronic airway inflammation

1. **Respiratory symptoms** (wheeze, dyspnoea, chest pressure, cough), vary in time and intensity

2. **Variable** expiratory airflow obstruction

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GINA: Global Initiative for Asthma: www.ginasthma.org
Manifestations of asthma

• Dyspnoea
  • acute or chronic
  • at rest or exercise-related
  • sometimes trigger
  • reversible
• Cough usually dry
• sometimes associated with allergies

Epidemiology

• 300 Mio asthmatics globally

• prevalence: 400 million 2025

• Significant morbidity & mortality despite effective Tx

• 1:250 deaths globally due to asthma

• Underdiagnosed and-treated (also high-income nations)

• CH: 10-12% children, 2-6% adults; prevalence allergic asthma increasing (D 2016: 10%)
Airways Inflammation in Asthma

Normal

Bronchial Mucosa

Bronchial wall (smooth muscle, connective tissue)

Asthma

Oedema
Mucus production
Muscle contraction

Asthma Exacerbation

Mucus lines the bronchial tubes
Inflamed airway
Airway with trapped air
Excess mucus

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Asthma Diagnosis

- History and symptoms
- Examination
- Lung function testing
  - Spirometry
  - Peak expiratory flow (PEFR)
- Bronchial Hyperreactivity
- Allergy testing
Spirometry

Lung function measurement

Typical spirometric tracings

Note: Each FEV\textsubscript{1} represents the highest of three reproducible measurements
Treatment Strategies Asthma

**Pharmacological Therapy**

**STEP 1**
- low-dose ICS
- Low-dose Theophylline

**STEP 2**
- low-dose ICS/LABA*
- Leukotriene Receptor Antagonist (LTRA)
- On-demand SABA or low-dose ICS/formoterol

**STEP 3**
- Interm/high dose ICS/LABA
- On-demand SABA or low-dose ICS/formoterol

**STEP 4**
- Interm/high dose ICS/LABA
- On-demand SABA or low-dose ICS/formoterol

**STEP 5**
- Add-on therapy e.g. Anti-IgE, Anti IL-5

<table>
<thead>
<tr>
<th>Controller</th>
<th>ICS</th>
<th>OCS</th>
<th>LABA</th>
<th>LAMA</th>
</tr>
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<tbody>
<tr>
<td>Treatment</td>
<td>ICS</td>
<td>OCS</td>
<td>LABA</td>
<td>LAMA</td>
</tr>
<tr>
<td>controller</td>
<td>inhaled corticosteroids</td>
<td>oral corticosteroids</td>
<td>long-acting β2 agonist</td>
<td>long-acting anti-cholinergic</td>
</tr>
</tbody>
</table>

**GINA 2018**

www.ginasthma.org
**Syndrome, Phenotypes & Endotypes**

- **Asthma Syndrome**
  - Variable symptoms, expiratory airflow limitation, bronchial hyper-reactivity, inflammation

- **Phenotypes**
  - Observed characteristics
  - Clinical presentation
  - Trigger
  - Response to therapy

- **Endotypes**
  - Functional or physiopathologic mechanisms (link between clinical characteristics and molecular pathways)

**Molecular Pathways in Allergic Asthma**

Biologics in Allergic Asthma

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</tr>
<tr>
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<td>Anti IL-13</td>
</tr>
<tr>
<td>Pitrakinra</td>
<td>Anti IL-4</td>
</tr>
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</table>

Omalizumab: Exacerbations

*Severe exacerbation defined as reduction in PEF or FEV1 to <60% of personal best and requiring treatment with systemic corticosteroids*

Humbert M et al., Allergy, 2005, Mar;60(3):309-16.
### Omalizumab: Treatment Duration

<table>
<thead>
<tr>
<th>Number Exacerbation-Free 1 year after Discontinuation</th>
<th>Omalizumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>n= 88</td>
<td>67.0%</td>
<td>47.7%</td>
</tr>
</tbody>
</table>

=50% exacerbation-free 1 year after discontinuation 5-year treatment

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### Biologics in Allergic Asthma

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<td>Dupilumab</td>
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www.clinicaltrials.gov, NCT01125748 (Results available)
**Mepolizumab (Anti-IL-5)**

Severe Asthma:
- frequent exacerbations >5/yr
- ICS > 1000 mcg BDP
- 55% OCS
- Sputum eosinophilia >5%
- FEV1 78%

Duration 1 Jahr
Mepolizumab 750mg/month iv.

Annual exacerbation rates
Placebo (n=32): 5 \(\rightarrow\) 3.2 Mepolizumab (n=29): 5.5 \(\rightarrow\) 2.0 *

FEV1: unchanged
AQLQ: difference 0.55 *

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**Mepolizumab (Anti-IL-5)**

Severe eosinophilic asthma:
- frequent exacerbations >3.5/yr
- ICS > 880 mcg FP
- 25% OCS
- blood eosinophilia > 0.28 G/L
- FEV1 <65%

Duration 28 weeks
Mepo 75mg iv. u. 100mg/Monat sc

Annual exacerbation rate:
Placebo (n=191): 3.6 \(\rightarrow\) 1.75
Mepo 75mg iv (n=191): 3.5 \(\rightarrow\) 0.91 **
Mepo 100mg sc (n=194): 3.8 \(\rightarrow\) 0.83 **

FEV1: \(\Delta +146\text{ml (iv)}, +136\text{ml (sc)} \)**
AQLQ: \(\Delta 0.42 \text{(iv), 0.44 (sc)} \)**
**Mepolizumab (Anti-IL-5)**

Severe asthma treated with OCS:
- frequent exacerbations >2.9/yr
- ICS > 880 mcg FP
- Median OCS Dose >12mg/d
- Blood eosinophilia > 0.23 G/L
- FEV1 <60%

Duration 20 wks Mepo 100mg/month sc

↓ median OCS Dose:
0% PL, -50% Mepo

Annual exacerbation rate:
Placebo (n=66): 2.9 → 2.12
Mepo 100mg sc (n=69): 3.3 → 1.44 *

FEV1: Δ + 128ml NS
ACQ-5: Δ 0.52 **

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**Benralizumab (Anti-IL5R): Exacerbations**

Subgroup ≥ 300 Eos/µL

**SIROCCO (48 weeks)**

<table>
<thead>
<tr>
<th>N= 267</th>
<th>275</th>
<th>267</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual exacerbation rate</td>
<td>1.33</td>
<td>0.73</td>
</tr>
</tbody>
</table>

**CALIMA**

<table>
<thead>
<tr>
<th>N= 248</th>
<th>241</th>
<th>239</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual exacerbation rate</td>
<td>0.93</td>
<td>0.6</td>
</tr>
</tbody>
</table>

The background exacerbation rate of 0.93 in the CALIMA study was lower than expected

Benralizumab (Anti-IL5R): Exacerbations

**Subgroup: ≥ 3 Exacerbations, ≥ 300 Eos/µL**

**SIROCCO (48 weeks)**

-57%**

**CALIMA (56 weeks)**

-51%*

-52%*

*P≤0.005

**P≤0.0005

*Data for CALIMA from high-dosage ICS cohort


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**Benralizumab (Anti-IL5R): Exacerbations**

### SCIROCCO Eos <300

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Treatment</th>
<th>Delta</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>2.70</td>
<td>1.21</td>
<td>1.49</td>
</tr>
<tr>
<td>Q4W</td>
<td>2.70</td>
<td>0.85</td>
<td>1.85</td>
</tr>
<tr>
<td>Q8W</td>
<td>2.60</td>
<td>1.00</td>
<td>1.60</td>
</tr>
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### SCIROCCO Eos >300

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<th>Treatment</th>
<th>Delta</th>
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<tbody>
<tr>
<td>Placebo</td>
<td>3.10</td>
<td>1.33</td>
<td>1.77</td>
</tr>
<tr>
<td>Q4W</td>
<td>3.00</td>
<td>0.73</td>
<td>2.27</td>
</tr>
<tr>
<td>Q8W</td>
<td>2.80</td>
<td>0.65</td>
<td>2.15</td>
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### CALIMA Eos <300

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<tr>
<td>Q4W</td>
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<td>0.78</td>
<td>1.82</td>
</tr>
<tr>
<td>Q8W</td>
<td>2.70</td>
<td>0.73</td>
<td>1.97</td>
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### CALIMA Eos >300

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<td>1.87</td>
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<td>2.80</td>
<td>0.60</td>
<td>2.20</td>
</tr>
<tr>
<td>Q8W</td>
<td>2.70</td>
<td>0.66</td>
<td>2.04</td>
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Benralizumab (Anti-IL5R): Lung Function

SIROCCO (48 weeks)\(^1\)

- Placebo
- Benralizumab Q4W
- Benralizumab Q8W

CALIMA\(^a\) (56 weeks)\(^2\)

- Placebo
- Benralizumab Q4W
- Benralizumab Q8W

* \(\text{P}<0.05\)
** \(\text{P}<0.01\)

\(\text{N}=\) 261, 271, 264

\(\text{N}=\) 244, 238, 238

- Data for the CALIMA study is from high-dosage inhaled corticosteroid cohort.


Benralizumab (Anti-IL5R): Symptoms

SIROCCO (48 weeks)\(^1\)

- Placebo
- Benralizumab Q4W
- Benralizumab Q8W

CALIMA\(^a\) (56 weeks)\(^2\)

- Placebo
- Benralizumab Q4W
- Benralizumab Q8W

- Asthma symptoms: wheeze, chest tightness, shortness of breath, and cough

* \(\text{P}<0.05\)
** \(\text{P}<0.01\)

\(\text{N}=\) 267, 273, 263

\(\text{N}=\) 248, 241, 239

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**Lebrikizumab (Anti-IL-13)**

- Severe exacerbations 0.27/yr
- ICS 580 mcg FP (60% >500)
- FEV1 65%

Duration 8 months
Lebrikizumab 250mg/month sc

high Periostin (HP): Plac 59, Lebr 51
low Periostin (LP): Plac 50, Lebr 51

FEV1: HP Δ +8.2% *
LP Δ +1.6%

Severe exacerbations week 24:
HP: 0.25 → 0.08 (Δ -67%)*
LP: 0.33 → 0.24 (Δ -29%)

ACQ-5: HP Δ - 0.03
LP Δ - 0.04

Dupilumab (Anti-IL-4R)


Mean baseline eosinophil count (eosinophils per µL)

<table>
<thead>
<tr>
<th>Eosinophils per µL</th>
<th>Mean</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>347 (46 - 477)</td>
<td>590 (59 - 572)</td>
<td>172 (69 - 90)</td>
<td></td>
</tr>
</tbody>
</table>

Mean baseline total IgE (IU/mL)

<table>
<thead>
<tr>
<th>IgE</th>
<th>Mean</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>435 (153 - 883)</td>
<td>358 (191 - 661)</td>
<td>345 (18 - 518)</td>
<td></td>
</tr>
</tbody>
</table>

Mean number of asthma exacerbations in past year

<table>
<thead>
<tr>
<th>Exacerbations</th>
<th>Mean</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.37 (1-4-7)</td>
<td>2.37 (2-3-4)</td>
<td>2.02 (1-4-8)</td>
<td></td>
</tr>
</tbody>
</table>

High-dose inhaled corticosteroid plus long-acting β₂-agonist* use

<table>
<thead>
<tr>
<th>Use</th>
<th>Mean</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>314 (55%</td>
<td>174 (36%</td>
<td>210 (43%</td>
<td></td>
</tr>
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<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>Median</th>
<th>Range</th>
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<tbody>
<tr>
<td>Mean age (years)</td>
<td>46 (12-84)</td>
<td>46 (12-84)</td>
<td>46 (12-84)</td>
</tr>
<tr>
<td>Male</td>
<td>286 (12%)</td>
<td>129 (6%)</td>
<td>129 (6%)</td>
</tr>
<tr>
<td>Race</td>
<td>White</td>
<td>107 (1%)</td>
<td>107 (1%)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>43 (44%)</td>
<td>43 (44%)</td>
<td>43 (44%)</td>
</tr>
<tr>
<td>Asian</td>
<td>15 (12%)</td>
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<td>15 (12%)</td>
</tr>
<tr>
<td>American Indian or Alaska Native</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Native Hawaiian or Other Pacific Islander</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (1%)</td>
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BIC 2018
Tezepelumab (Anti-TSLP)


Tezepelumab (Anti-TSLP)

Tezepelumab (Anti-TSLP)


IgE >100 IU/ml
blood Eos >0.14G/L
Phenotype-directed Asthma Therapy

Inflammation

- Eosinophilic
- Neutrophilic
- Neutrophilic Pauci-granulocytic
- Fixed Obstruction Hyperplasia bronchial smooth muscle
- Allergic
- Non-allergic

High-dose ICS Nasal ICS LTRA OCS
+ Low-dose Macrolide Antibiotic
+ Weight loss Female obese asthma
+ Bronchial Thermoplasty?

Biologics & Asthma

- Placebo-effect exacerbations (e.g. Mepolizumab: -27% to -51%)
- Study duration ≤1 yr (as short as 5 months)
- Eosinophilia @ inclusion: adherence ICS / OCS Therapy?
- Costs: Nucala® (Mepolizumab): ≈1'500,- / month, Benralizumab?