



HEALTHY LUNGS FOR LIFE



ERS



ELF

Emerging Drugs for COPD

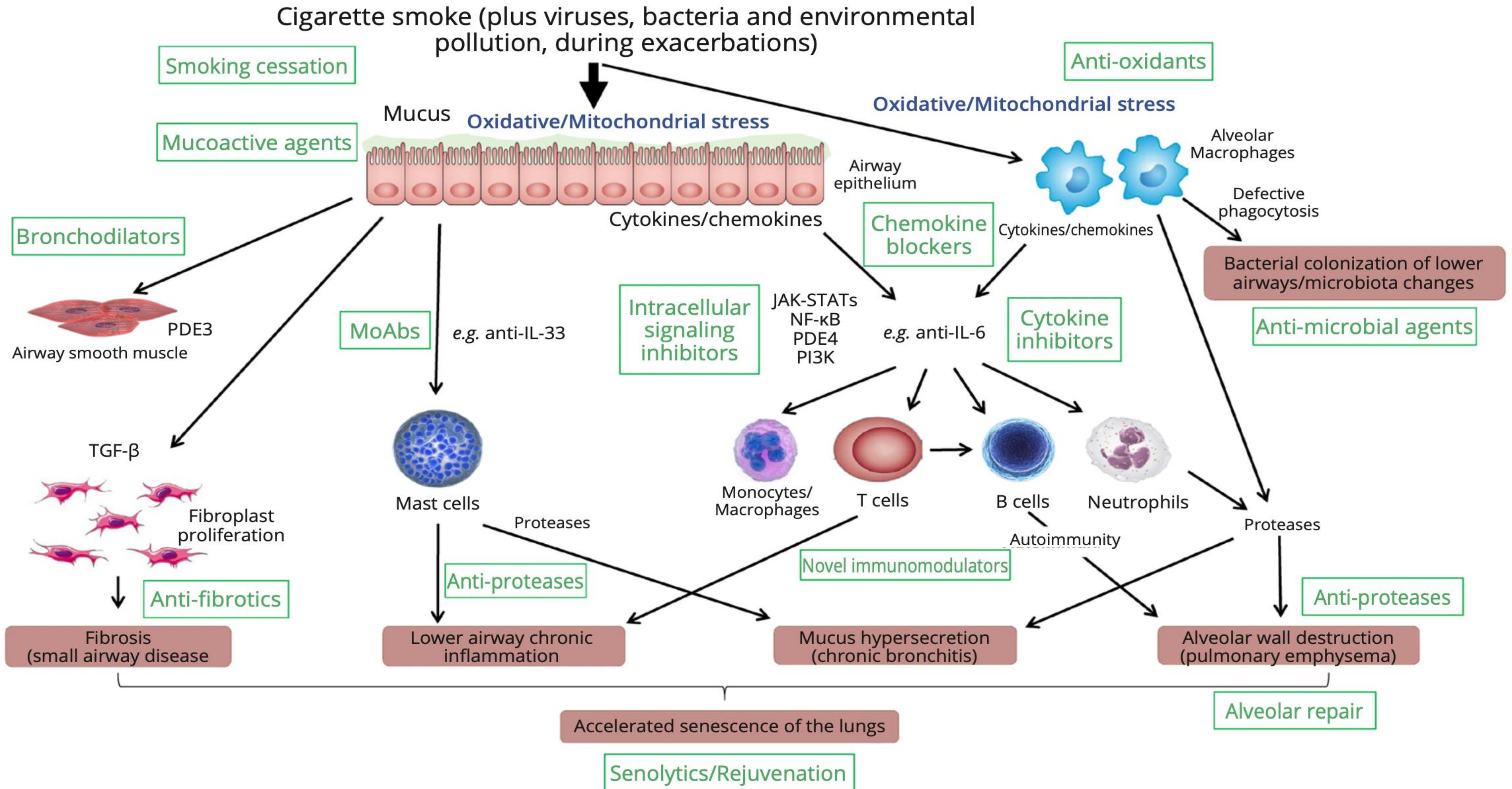
15/11/2022 Kowar Hospital

Current treatments for COPD

Classification

- Beta 2-adrenoceptor agonists
- Anticholinergics
- Methylxanthines
- Corticosteroids
- PDE-4 inhibitors
- Antileukotrienes
- Antibiotics

Emerging Targets for COPD



Drugs and COPD

- New therapies are multifaceted, including:
- 1) improvement of existing classes of drugs
- 2) development of novel therapies
- 3) identification of novel genetic targets

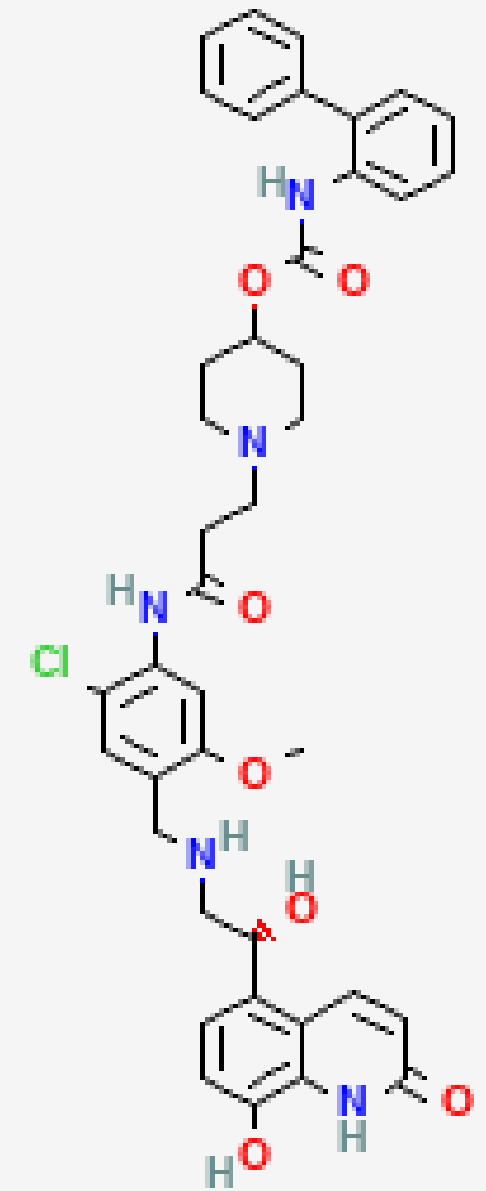
Improvement in current drugs

Investigational drugs

- New ultra long acting beta-2 agonist (ULABA): **Abediterol**
- In 70 COPD patients, abediterol significantly enhanced FEV₁ compared with placebo and significantly better than indacaterol (1).
- New inhaled glucocorticoids (ICS): **Valsecorat (AZD7594)** is a non-steroidal, selective, glucocorticoid receptor modulator (SGRM), once-daily
- *Proton et al, Drug Des Devel Ther 2019*: acceptable safety profile with limited impact on systemic markers of glucocorticoid activity (2).
- combined valsecorat and abediterol as a once daily fixed dose combination (NCT02967159, N.=14) is ongoing!

Dual action compounds (MABA)

- batenfenterol:
- NCT02570165 is finished on 325 stable patients but result are not reported yet
- Navafenterol:
- is another MABA; despite promising results in phases 1 and 2, most phase 3 studies have not published the results yet(4).



New inhaled PDE 4 and PDE 3/4 inhibitors

- CHF6001 is an *inhaled PDE4 inhibitor* that significantly suppressed leukocytes and neutrophils and IL-1 β , TNF- α , and G-CSF in mice
- It has good safety profile in healthy subjects
- Ensifentrine (RPL554) is dual inhibitor of phosphodiesterase PDE 3/4. It has profound bronchodilation effects with anti-inflammatory effects
- It could increase COPD QoL greater than tiotropium

Antioxidants and COPD

N-acetyl cysteine (NAC)

- Current findings are not satisfactory!
- The PANTHEON study: 600mg twice daily NAC for 1 year, did not delay the time to first exacerbation compared to untreated patients
- NAC (1200 mg daily for 7 days) added to standard care including 40 mg/day prednisolone failed to improve lung function
- Nanoparticles loaded with flavonoid significantly suppressed suppress the expression of LPS-induced IL-1 β , IL-6, TNF- α and iL-8 in lung cells

New anti-inflammatory drugs

- MABs and Small molecules
- Inflammation and COPD
- Current bans and questions

CANTOS trial 2017

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease

P.M. Ridker, B.M. Everett, T. Thuren, J.G. MacFadyen, W.H. Chang, C. Ballantyne,
F. Fonseca, J. Nicolau, W. Koenig, S.D. Anker, J.J.P. Kastelein, J.H. Cornel, P. Pais,
D. Pella, J. Genest, R. Cifkova, A. Lorenzatti, T. Forster, Z. Kobalava,
L. Vida-Simiti, M. Flather, H. Shimokawa, H. Ogawa, M. Dellborg, P.R.F. Rossi,
R.P.T. Troquay, P. Libby, and R.J. Glynn, for the CANTOS Trial Group*

MABs

- Our experience?
- A 6-month therapy with **Mepolizumab** (anti IL-5) significantly reduced sputum and blood eosinophils compared to placebo but had no effect on lung function, QoL scores, sputum markers or on the rate of exacerbations (10)
- **Anti IL-33** (AMG-282) in moderate-very severe COPD patients is ongoing (phase 2)
- **Tezepelumab** (MEdl9929 and AMG157) is a monoclonal antibody targeting human TSLP that is effective in severe asthma, still in phase 2 (NCT04039113)

Small molecules

Experimental agents

- (CAT-1004), an **oral NF- κ B inhibitor**, is now in phase 3 studies for Duchenne Muscular dystrophy following the successful completion of a phase 2 clinical trial (NCT02439216)
- (PF-06263276) **an inhaled Janus kinase (JAK)** inhibitor has been through preclinical studies and showed a dose-dependent suppression of IL 6-induced activity in mouse lung
- tofacitinib used in RA, has warnings for MACE

New protease inhibitors

- The release of neutrophil elastase (NE) from is important in COPD pathogenesis and progression
- Oral daily NE inhibitor alvelestat (MPH-996) is currently being investigated in two 12- week multicenter, double-blind, randomised, placebo-controlled studies (NCT03636347 and NCT03679598) in emphysematous patients with AAT deficiency (N.=165 and N.=66, respectively)
- Both studies will examine the effect on lung damage and disease progression

New anti-microbial agents

- Ribavirin (CCi15106, GlaxoSmithKline) by inhalation has investigated in 2 clinical trials either using capsules (NCT03243760) or as a powder (NCT03235726)
- Further studies are required to investigate the ability of inhaled powder ribavirin to suppress exacerbations of COPD
- MV130 is a cocktail of Gram+ and Gram– bacteria used as mucosal sublingual immunotherapy, MV130 appears to act through dendritic cell-mediated induction of Th1, Th17 and IL-10 responses
- A clinical trial of MV130 in COPD (NCT01842360) was completed in December 2020

Stimulating lung regeneration

ongoing investigations

- mesenchymal stem cells
- low level laser
- metered cryospray (liquid nitrogen)

Future drugs

- Targeting CD137 T cells
- P38 MAPK inhibitors
- Selectin antagonists
- Anti-IL-17A monoclonal antibodies
- α 1-Antitrypsin replacement therapy
- Dipeptidyl peptidase 1 inhibitors

Conclusions

- The current therapies for COPD do not reverse the hallmark features of disease. recognizing the heterogeneity of COPD patients
- The identification of the molecular mechanisms that define these COPD subphenotypes using state-of-the- art **omics** technology will lead to new approaches
- Greater insight towards novel processes and pathways of stable COPD and their exacerbations

Thank you very much