Where Are the Opportunities, Challenges in Airway Disease

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Collaborative research – Merck, Meso Scale, SRA, Sanofi
### Market Overview: Airway Disease

*Opportunities and Challenges*

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**Challenges:**
- Moving from Phenotype to Endotype
- Disrupting Paradigms/Rethinking Pathobiology
- Learning from both Academia and Industry
- Implementation
Opportunities and Challenges For Asthma

Asthma –
*Phenotype to Endotype (Clinical Criteria to molecular mechanisms)*
T2 – Treatment is now addressed with several molecules
Non-T2 mechanisms – Where’s the tractable biology?
Neutrophils – IL-6<sup>High</sup>/Infections/NETosis

*Revisiting the asthma paradigm for increased pro-inflammatory factors*
Non-inflammatory mechanisms/AHR
Defective Resolution mechanisms/SPMs

*Disease modification* - Next frontier is primary prevention
Preserving lung function, reducing exacerbations, inducing remissions
[All 3 require early intervention](#)

*Implementation* - Impact of the new 2019 GINA recommendations –
No SABA alone   [SABA with ICS prn or ICS-LABA combination](#)

Neutrophil cytoplasts induce TH17 differentiation and skew inflammation toward neutrophilia in severe asthma

Israel E, Reddel HK. NEJM 2017;377:965
Ideal Outcome of Acute Inflammation Is Complete Resolution

Revisiting Asthma Pathobiology

Is Severe Asthma A Resolution Failure?

COPD or COPS

Age 42, FEV₁ 38% predicted

Age 47, FEV₁ 20% predicted

Hersh CP, COPD 2007;4:331-7
Parenchymal Heterogeneity: GOLD Stage 1 COPD

FEV1: 85%  
FEV1: 82%  
FEV1: 88%

Images courtesy of George Washko
Vascular Heterogeneity: COPD

19% emphysema

$RV_{EV} = 58.9\text{mL}$

Arterial BV5: 131mL

18% emphysema

$RV_{EV} = 140\text{mL}$

Arterial BV5: 70.8mL

Images courtesy of George Washko
Opportunities and Challenges For COPD

COPD – *Phenotype to Endotype (Clinical Criteria to molecular mechanisms)*
COPD or COPS – Evident clinical heterogeneity
COPD gene
Dysregulated innate immune responses

Revisiting the COPD paradigm
Need more than bronchodilators
Links between inflammation matrix destruction and microbiome
Defective Catabasis

Disease modification -
Preserving lung function, reducing exacerbations, inducing remissions

All 3 require early detection (biomarkers) and intervention

2016, 5(F1000 Faculty Rev):2392 (doi:10.12688/f1000research.7018.1)

Barnes, P. J. et al. (2015) Chronic obstructive pulmonary disease
*Nat. Rev. Dis. Primers* doi:10.1038/nrdp.2015.76
COPDGene Phase 3

Genetic Findings in COPD

Network Analysis

Omics characterizations

- Imaging Data
- Clinical Data
- Gene Expression
- Whole Genome Sequencing
- Epigenetics
- Metabolomics
- Proteomics

Subjects

Images courtesy of Ed Silverman and James Crapo
Opportunities in Airway Disease:
Conceptual Framework of Endotypes Provides Stratification

Reduces large heterogenous syndromes into smaller cohorts
with aligned molecular mechanisms

Advances the field

Create smaller, potentially more tractable (?) opportunities for industry
Opportunities and Challenges For Cough:
“Itch of the airway” - mediated by nociceptors

- Prevalence of cough ranges from 5-40% of population
  - Single most common symptom prompting outpatient medical visits in US
- Labeled products show marginal benefit over placebo
- Pain medications and sodium channel blockers used to treat cough
  - Nebulized lidocaine is used for procedures, in severe chronic cough patients as well as in the military

Cough –
Lessons from challenges in industry (Value of industry-academic partnerships)
Rethinking the paradigm
Nociceptor Activation in Cough: Large Pore Channels

Nociceptor Activation in Cough: Multiple Approaches

- **NaV Inhibition**: Lidocaine, tetracaine, benzocaine
- **Large Pore Antagonists**: P2X2/3; P2X3; TRPA1; TRPV4
- **Anti-inflammatory**
- **CNS Agents**

PERIPHERAL TERMINAL

Receptor potential

Noxious stimuli

- TRPA1
- TRPM8
- ASIC
- TRPV1-4
- 5-HT
- P2X
- TRKA
- GPCRs
Nociceptor Silencing – Charged Sodium Channel Blockers

CSCB or “Nocion”

Blocks sodium channel

Nocions

- **Longer-acting**, potential for QD/BID dosing
- **Locally selective**, not passively cell permeable
- Topical; **minimal systemic redistribution**
- Broad and **potent** Na<sub>v</sub> inhibition
- No TRPA1 / TRPV1 agonism
- In vivo data in cough, itch, surgical pain, atopic dermatitis
- Novel composition of matter
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Opportunities and Challenges

Major Airway Diseases:
- Asthma
- COPD
- Cough

Opportunities:
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- Mitigating Symptoms (Exacerbations)
- Disease Modification (Loss of Lung Function/Cure)
- Leveraging Technology (New sensors/drug delivery/ AI)

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