Where Are the Opportunities, Challenges in Airway Disease

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Respiratory Innovation Summit

ATS International Conference

May 17, 2019

Disclosures: licensed patents – Propeller Health
Equity – Nocion Therapeutics, Entrinsic Health
Consulting – AstraZeneca, Bayer, Corbus Pharmaceuticals, Gossamer Bio, Entrinsic Health, MedImmune, Merck, Metera Pharmaceuticals, Nocion Therapeutics, Novartis, Pieris Pharmaceuticals, Sanofi, Teva Pharmaceuticals
Collaborative research – Merck, Meso Scale, SRA, Sanofi

Market Overview: Airway Disease

Opportunities and Challenges

Major Airway Diseases:

Asthma

COPD

Cough

Opportunities:

Precision Medicine

Mitigating Symptoms (Exacerbations)

Disease Modification (Loss of Lung Function/Cure)

Leveraging Technology (New sensors/drug delivery/ AI)

Challenges:

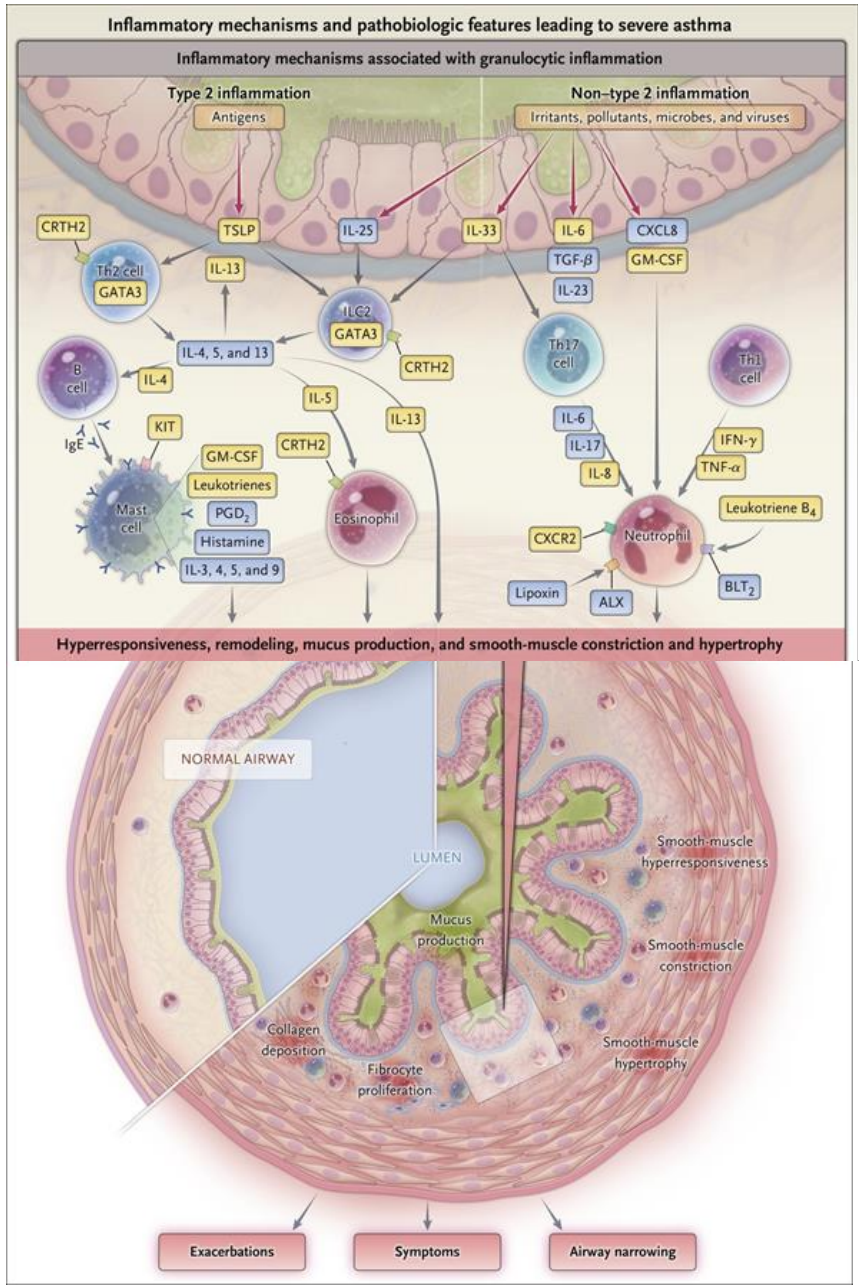
Moving from Phenotype to Endotype

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^{High}/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

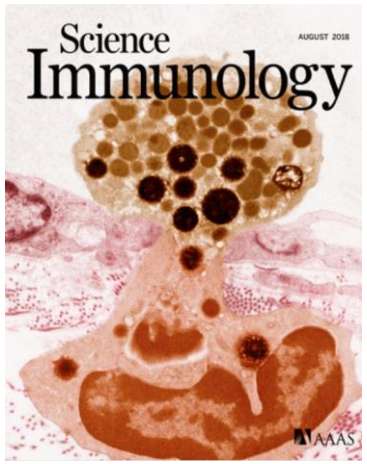
⇨ All 3 require early intervention

Implementation - Impact of the new 2019 GINA recommendations –

No SABA alone ⇨ SABA with ICS prn or ICS-LABA combination

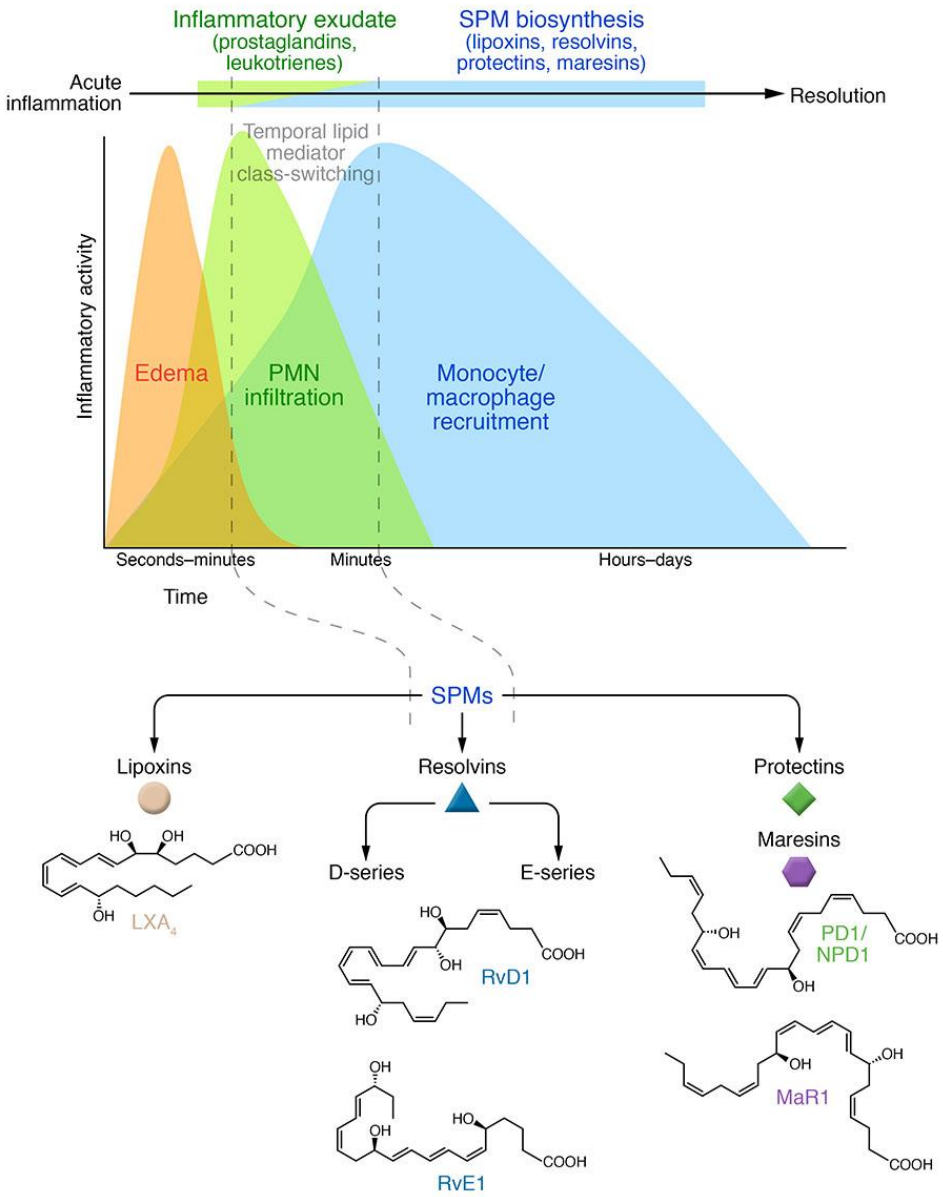
Israel E, Reddel HK. NEJM 2017;377:965

The NEW ENGLAND JOURNAL of MEDICINE



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

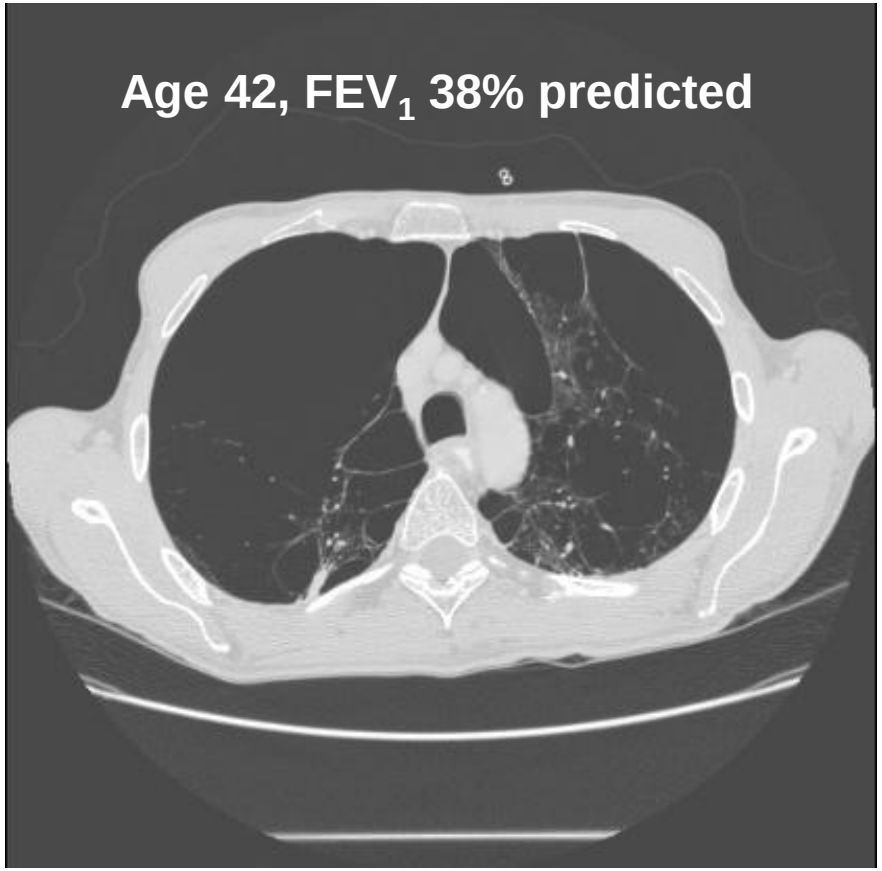
Ideal Outcome of Acute Inflammation Is Complete Resolution

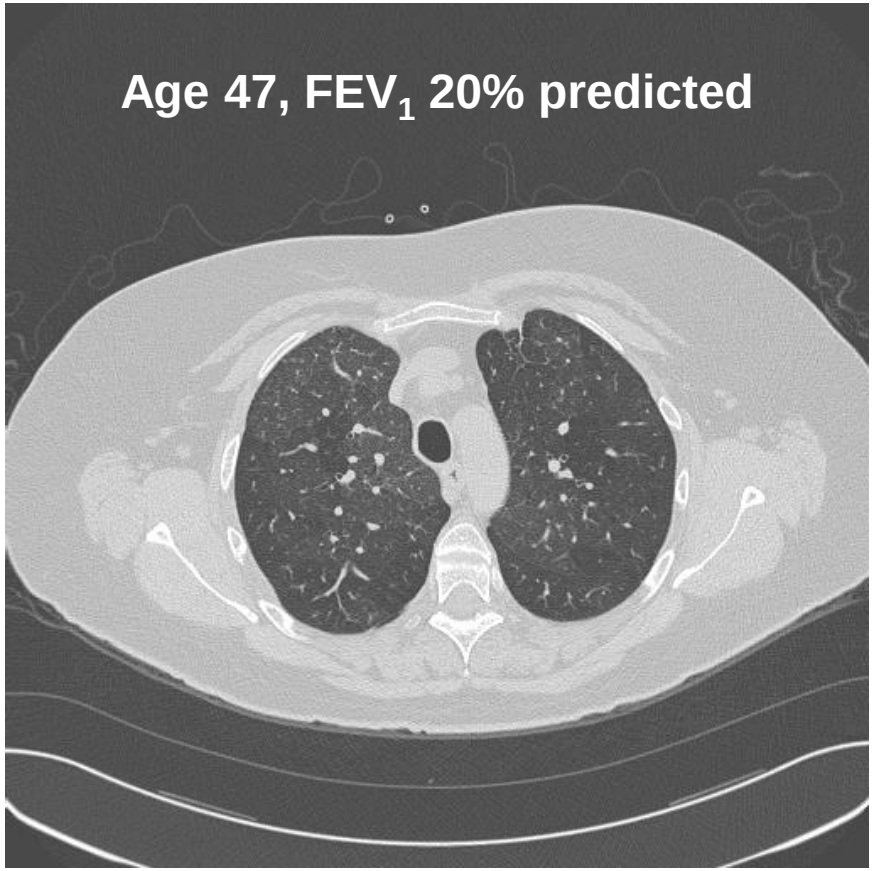


Revisiting Asthma Pathobiology

J. Clin. Invest. May 14, 2018.

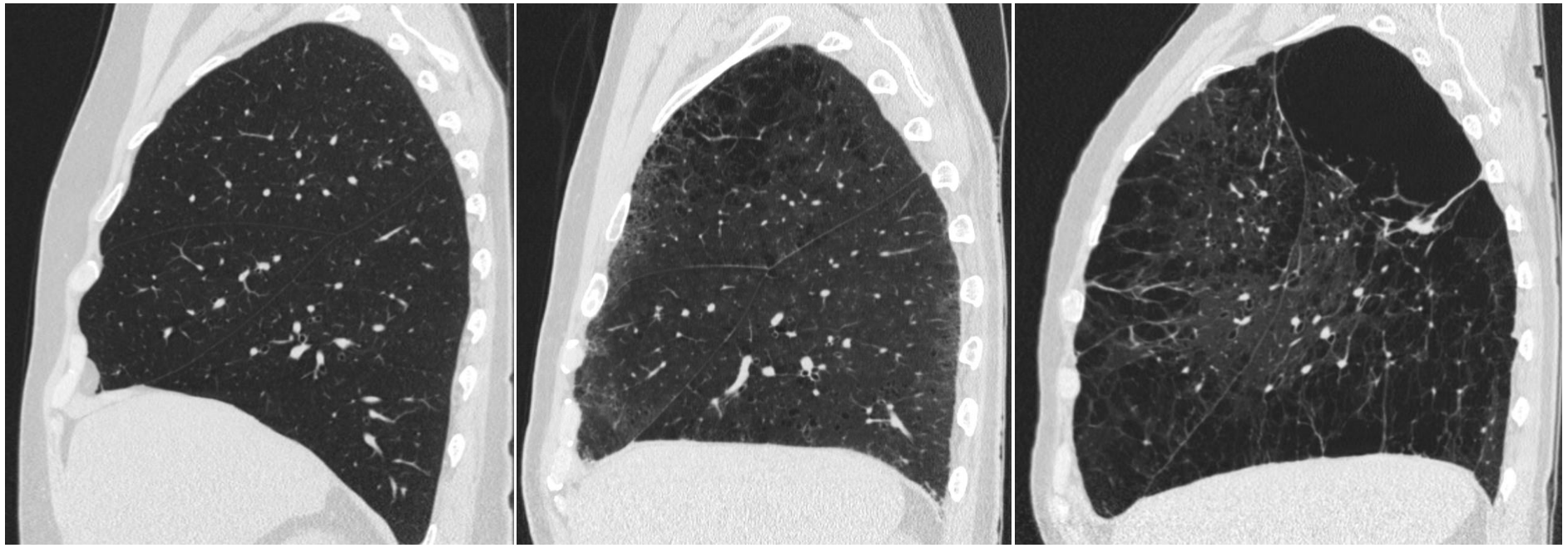
COPD or COPS





Hersh CP, COPD 2007;4:331-7

Parenchymal Heterogeneity: GOLD Stage 1 COPD



FEV1: 85%

FEV1: 82%

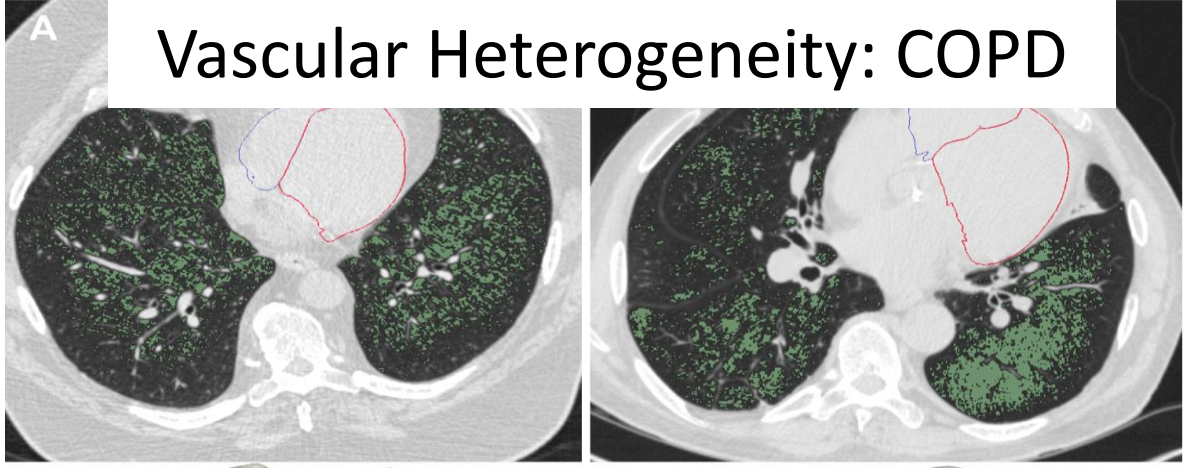
FEV1: 88%

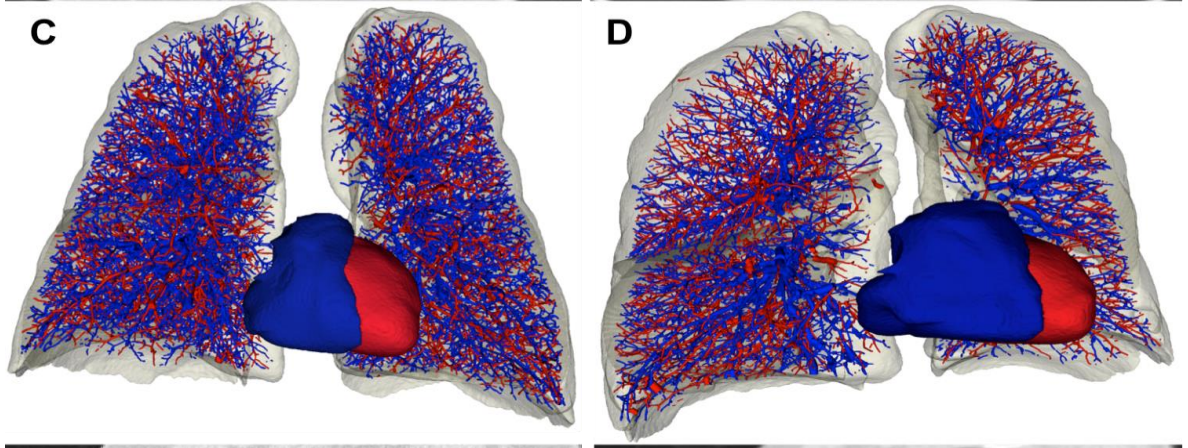
Images courtesy of George Washko

Vascular Heterogeneity: COPD

19% emphysema

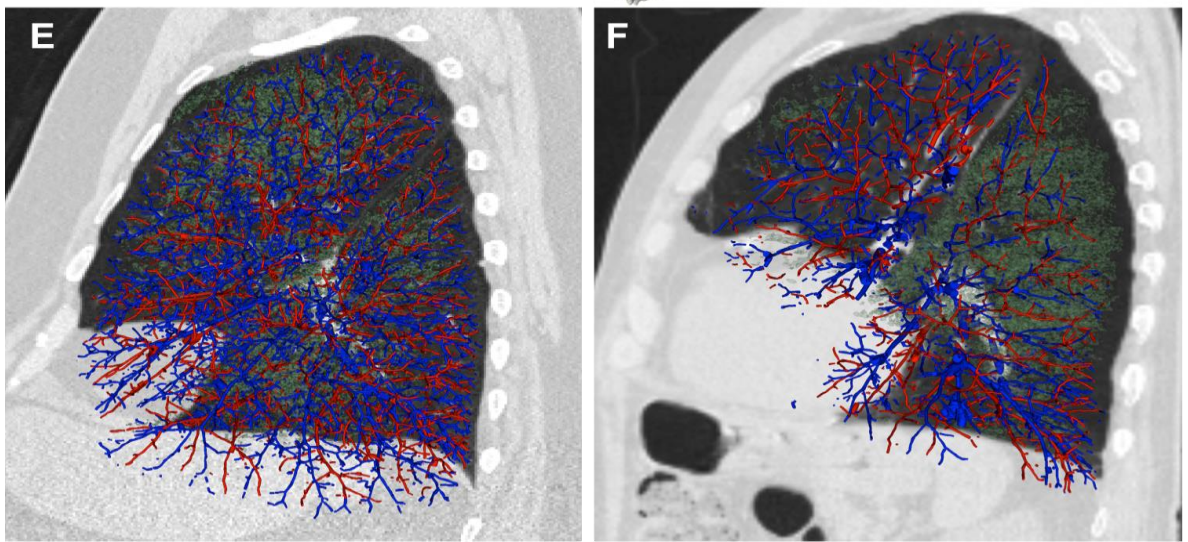
18% emphysema





RV_{EV}: 58.9mL

RV_{EV}: 140mL



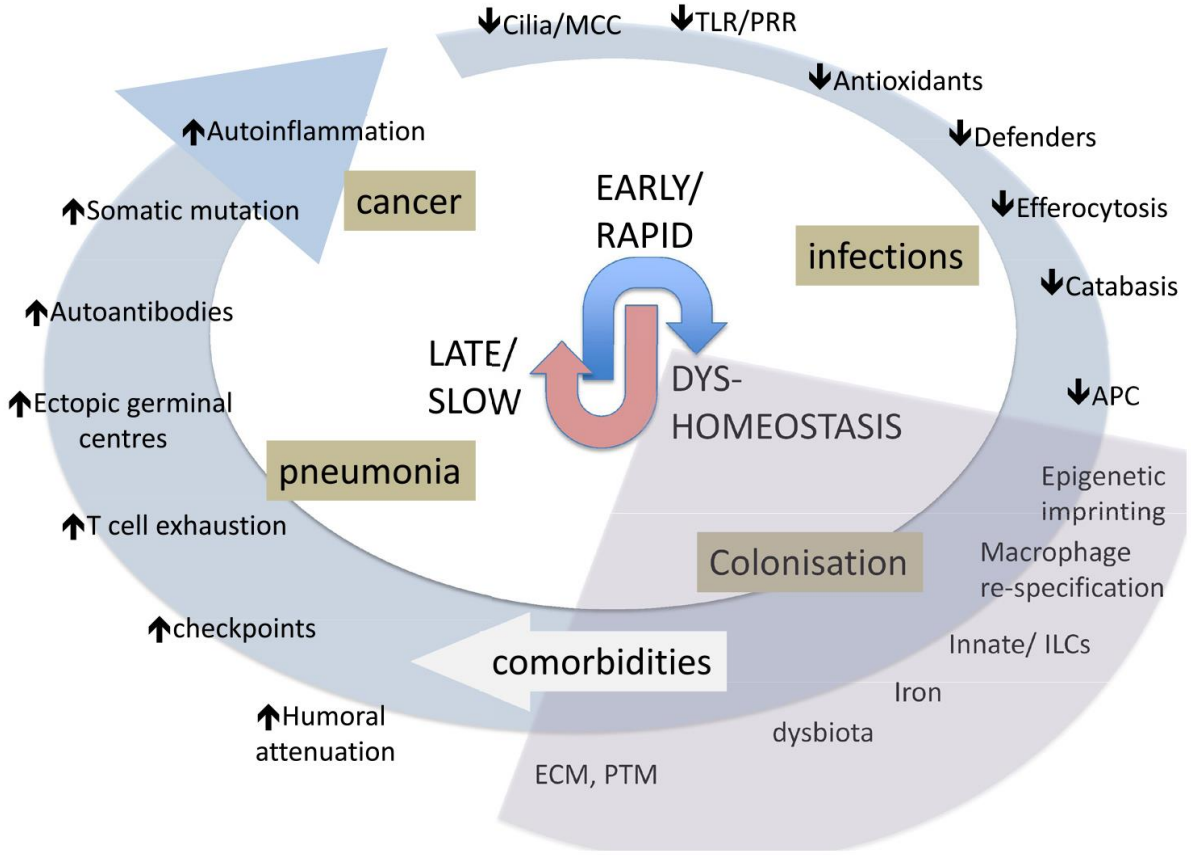
Arterial BV5: 131mL

Arterial BV5: 70.8mL

Images courtesy of George Washko

Opportunities and Challenges For COPD

Smoke Damages Immunity From Almost the First Exposure



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

<u>COPD</u> –

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

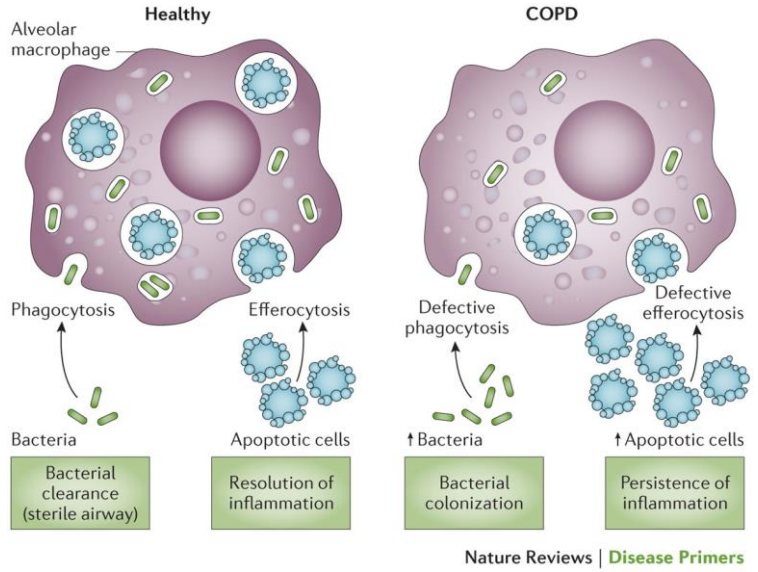
Links between inflammation matrix destruction and microbiome

Defective Catabasis

Disease modification -

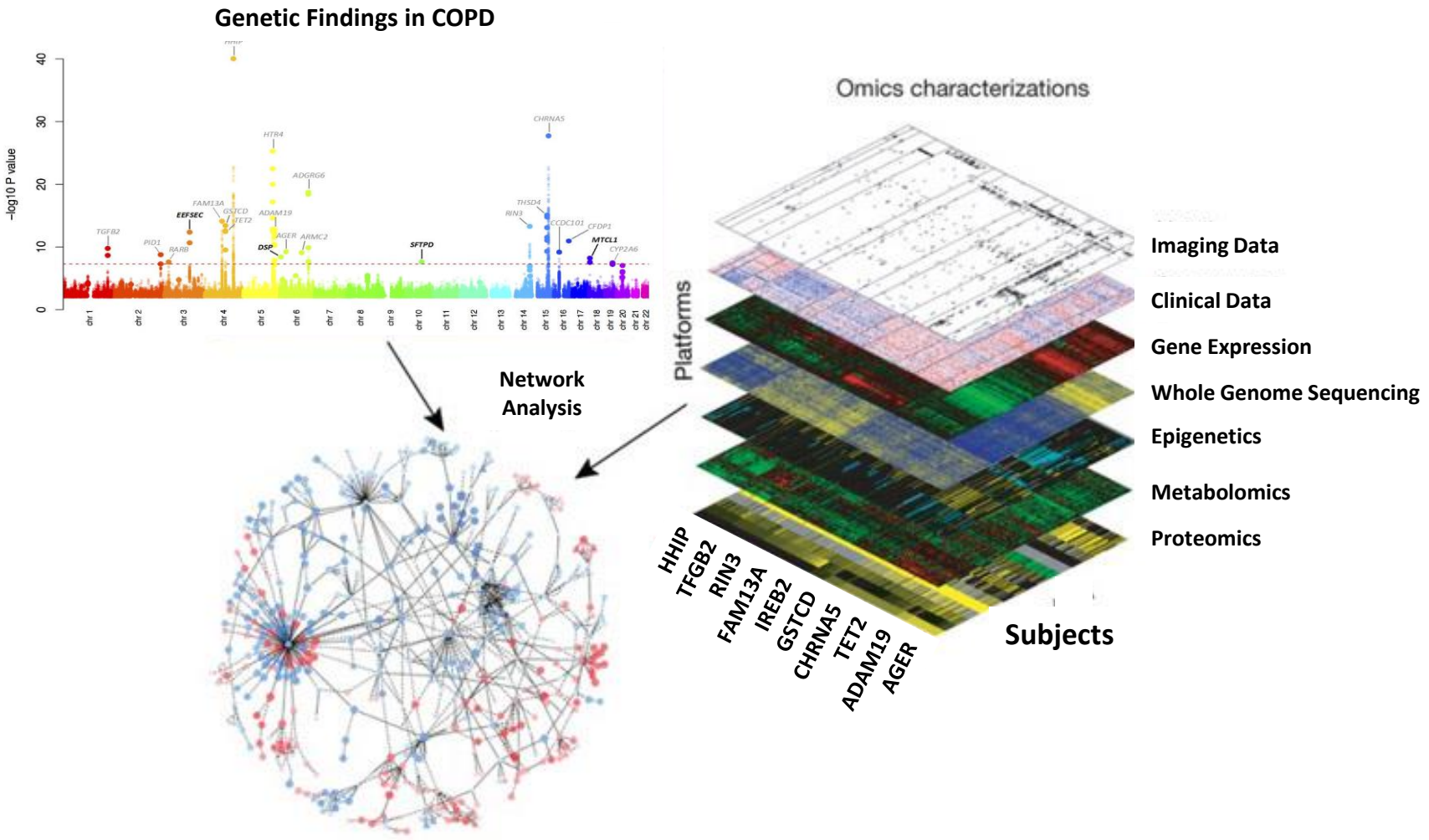
Preserving lung function, reducing exacerbations, inducing remissions

⇨ All 3 require early detection (biomarkers) and intervention



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

COPDGene Phase 3



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

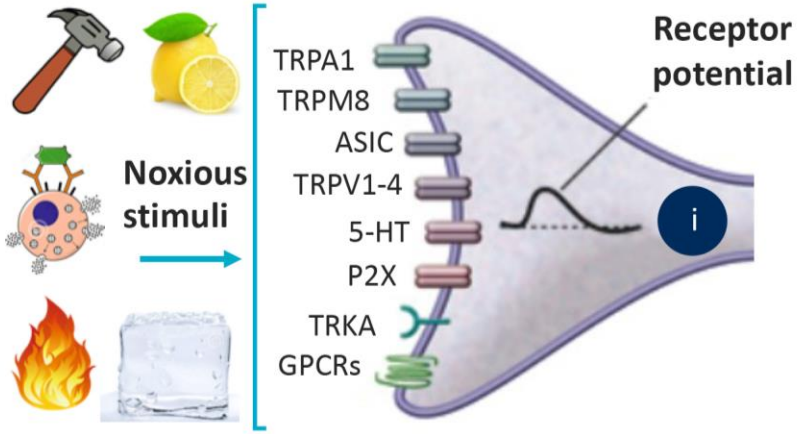
nocion THERAPEUTICS

Cough –

Lessons from challenges in industry (Value of industry-academic partnerships)
Rethinking the paradigm

Nociceptor Activation in Cough: Large Pore Channels

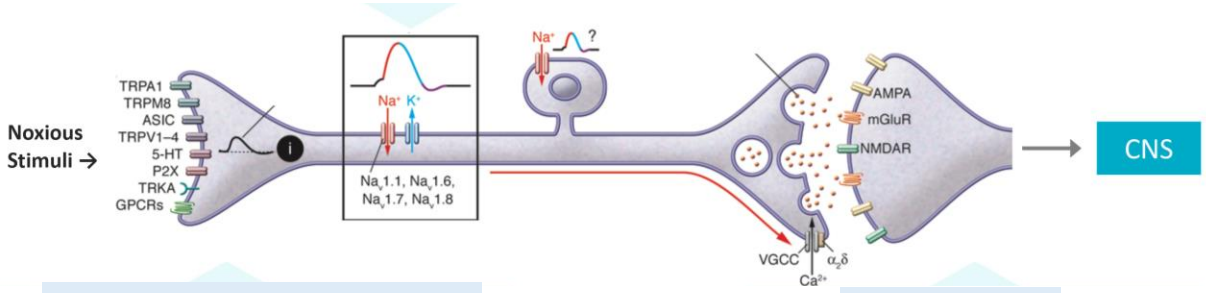
PERIPHERAL TERMINAL



Nociceptor Activation in Cough: Multiple Approaches

Anti-inflammatory

NaV Inhibition
Lidocaine, tetracaine, benzocaine



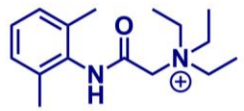
Large Pore Antagonists
P2X2/3; P2X3; TRPA1; TRPV4

CNS Agents

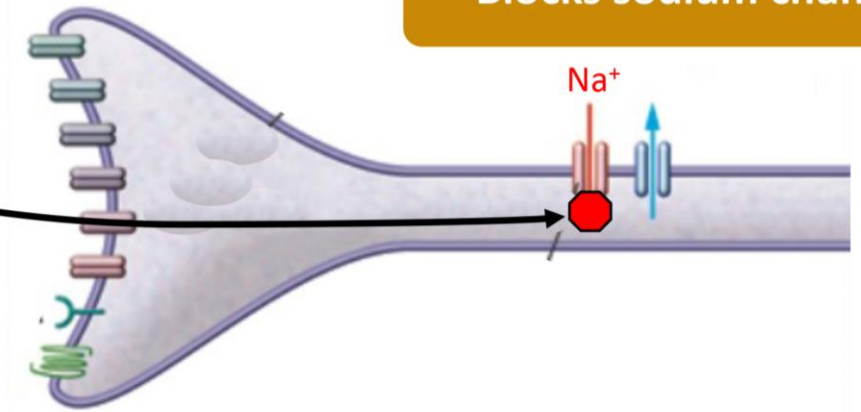
nocion THERAPEUTICS

Nociceptor Silencing – Charged Sodium Channel Blockers

CSCB or "Nocion"



Blocks sodium channel



Gains internal access to activated nociceptor through any open large-pore channel

Nocions

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

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