CONFIDENTIAL

The Centre for Drug Research and Development (CDRD)

Transforming Discovery into Opportunity

Allergen NCE: Planning for Research Success Series

Knowing Your Customer

December 1st, 2015

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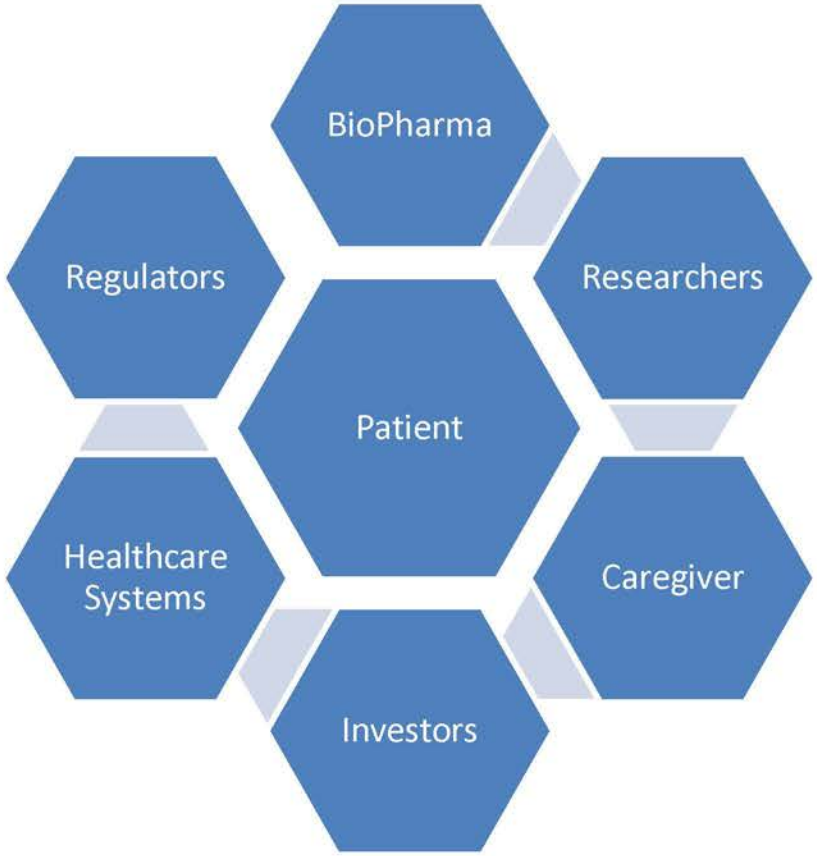
cdrd The Centre for Drug Research and Development
Transforming Discovery into Opportunity

AllerGen
Allergy, Genes and Environment Network

Who Are Your Customers?



Product Market Assessment

- Market assessment of a new technology
  - What is the mechanism?
  - What diseases does this pathway effect?
  - If you inhibit or stimulate this pathway how would it change the disease?
  - The number of patients who may benefit
  - Unmet need
  - Competitive landscape
  - Pricing
  - Regulatory Pathway
  - Health Economics
  - Payor Assessment

Asthma Unmet Needs

- The majority of patients respond to steroids and b-agonists, but ~10% of patients with severe asthma could use improved treatments
- Asthma is a heterogeneous disease but researchers have identified potential targets for patients with severe asthma based on the drivers of the immune response
  - Xolair: anti IgE antibody (Genentech/Roche 2003)
  - Nucala: anti IL-5 antibody (GSK 2015)
  - Benralizumab: anti IL-5 (PHIII positive results 2016)
  -

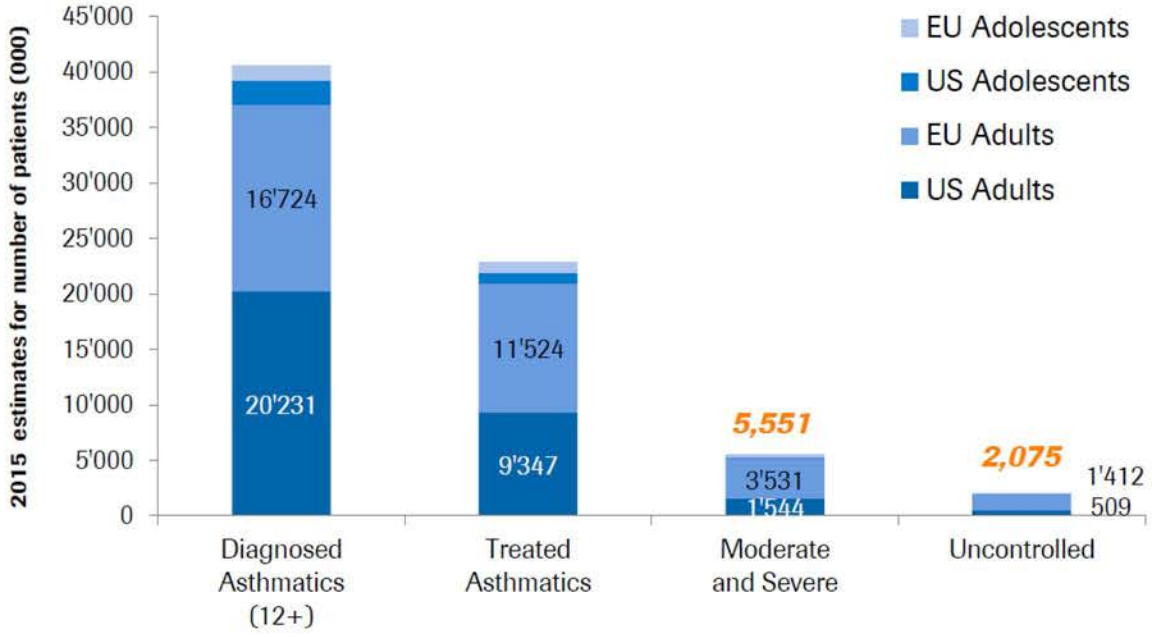
Asthma Market

- Asthma market estimated to be in the range of $18 to $20 Billion per year
- Largely generic but branded products available for severe asthma
  - Xolair sales over $2B (~$600M in Asthma) per year through Novartis and Roche
- New products to treat severe eosinophilic asthma from AZ, Teva, and GSK

http://www.fiercebiotech.com/biotech/astrazeneca-s-first-asthma-biologic-hits-phiii-target-but-still-behind-rivals
http://www.pmlive.com/pharma_news/teva_set_for_fda_verdict_on_reslizumab_early_next_year_758467

Patient Populations

Xolair, Lebrikizumab: Moderate to Severe Asthma



Source: Roche/Genentech

Reimbursement: Ontario Exceptional Access Program Asthma

ASTHMA

DRUG NAME	BRANDS REIMBURSED	DOSAGE FORM/ STRENGTH	REIMBURSEMENT CRITERIA (Refer to pages 2 to 4 for general disclaimers regarding the EAP funding criteria.)	STANDARD APPROVAL DURATION
Leukotriene Receptor Antagonists				
Zafirlukast	Accolate	20 mg tablet	**For the treatment of asthma patients who cannot manage the use of an inhalation** device despite assistance with a spacer (e.g. physically or mentally disabled patients or pediatric patients). OR **For the treatment of asthma in children and adolescents whose asthma cannot be controlled on ICS alone** and where the condition remains uncontrolled despite using full doses of ICS with addition of LABA, and with assurance of good adherence and inhaler technique **Renewal** of requests that meet the above criteria will be provided where the following apply: • Current medications and dosages must be clearly specified; AND • Objective evidence of positive response from treatment (spirometry OR decrease in health care utilization) must be provided	Initial: 5 years Renewal: 5 years
Montelukast	Singulair	5 mg, 10 mg tablet		Initial: 5 years (up until age of 18) Renewal: 5 years (up until age of 18)
Omalizumab	Xolair	150 mg/ vial	**For the treatment of severe uncontrolled asthma** in patients who meet the following criteria: • Has required hospitalization for asthma within the past 12 months; OR • Has required two or more urgent visits for asthma to a physician or an emergency department within the past 12 months; OR	Initial: 1 Year

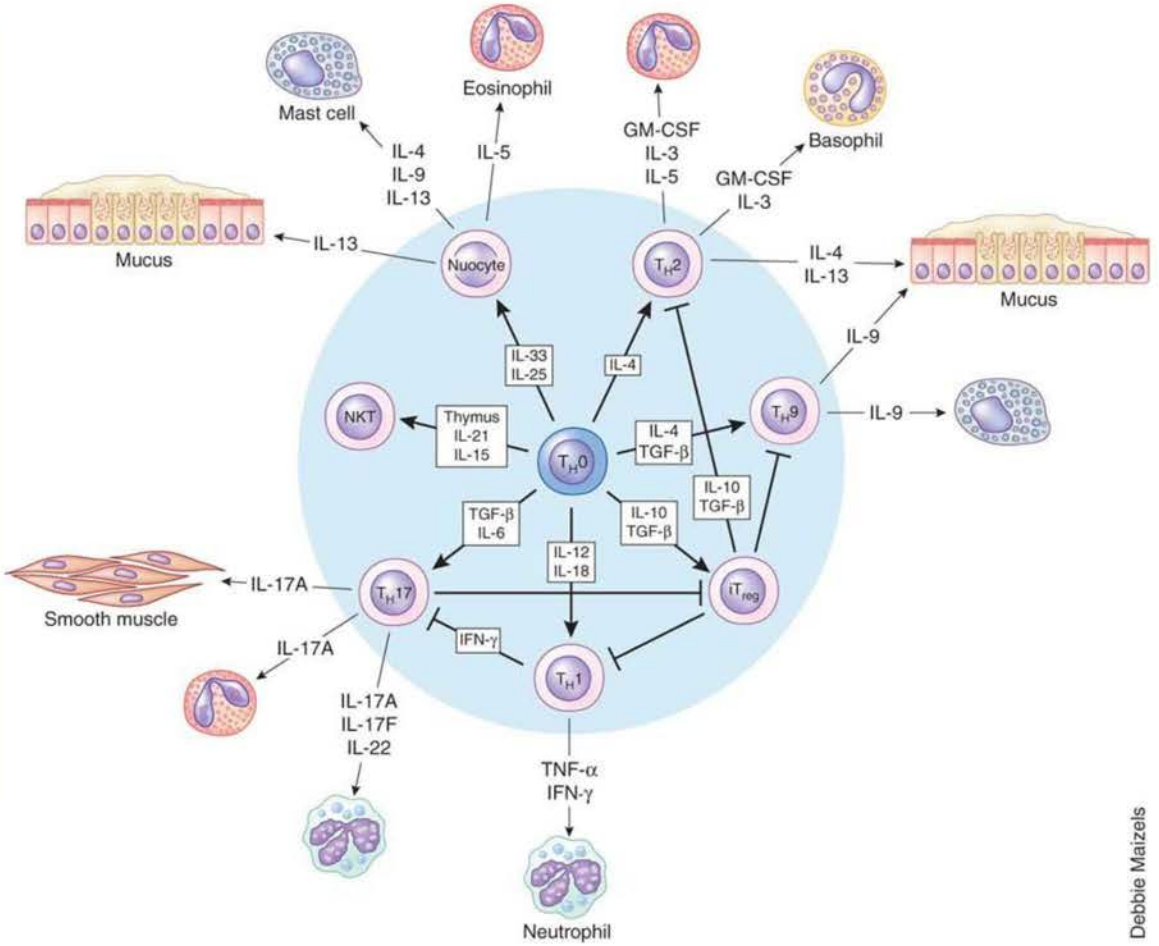
Pricing/Reimbursement

Source: http://www.nytimes.com/2013/10/13/us/the-soaring-cost-of-a-simple-breath.html?pagewanted=all&_r=0

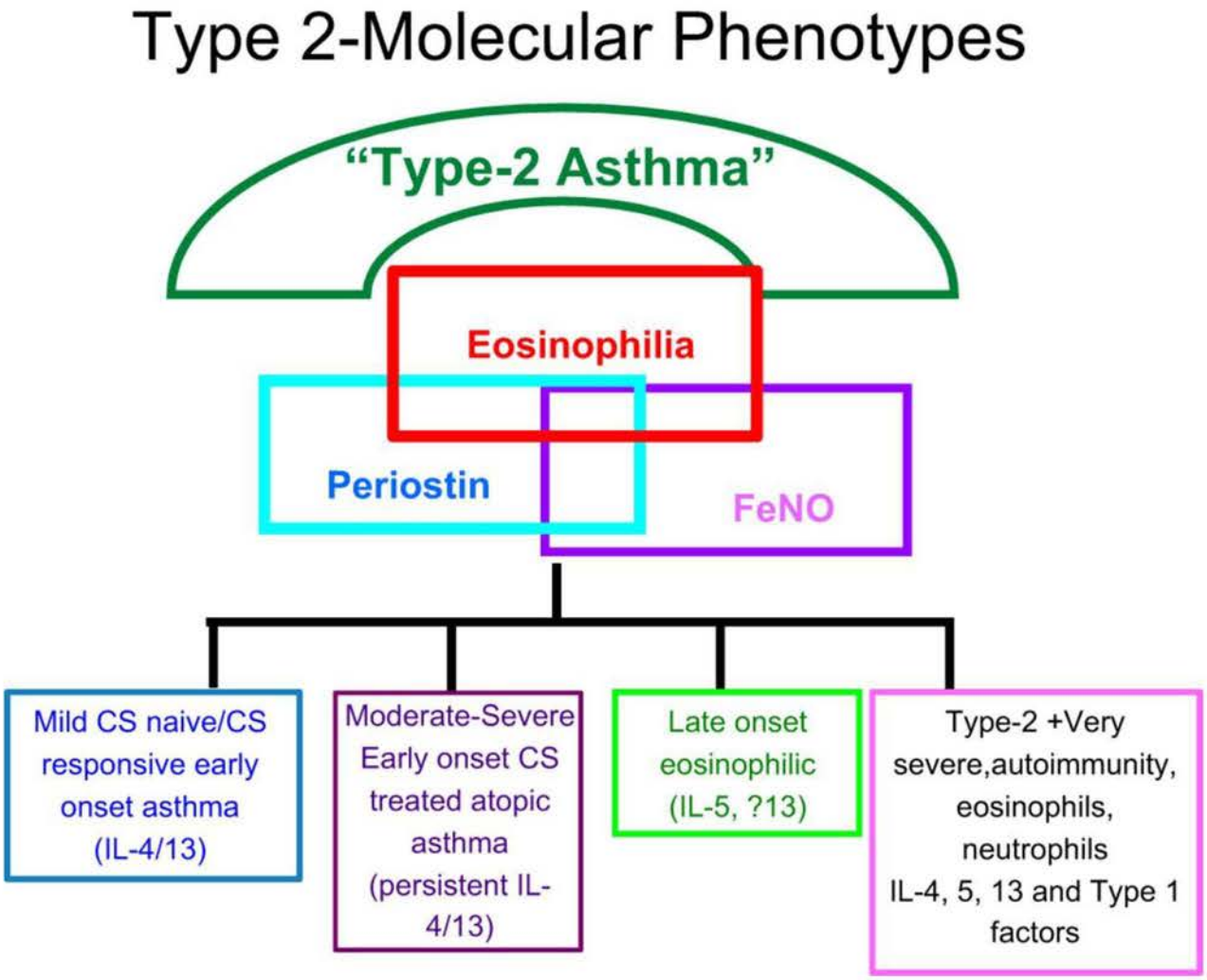
Asthma Effector Cells Overview

Potential Targeted Treatments

IL-17 Ab from Medimmune
Anti-TNF-α trial in asthmatics had modest results
IL-18 Ab in Dev for IBD & T2DM (GSK)
IL-13 Ab for TH2 Asthma from Roche & Medimmune
IL-5 Ab (multiple) for eosinophilic asthma
IL-9 Ab from Medimmune



The increasingly granular umbrella for Type 2 cytokine-associated asthma molecular phenotypes, all of which encompass some Type 2 inflammatory biomarkers.



Anuradha Ray et al. Am J Physiol Lung Cell Mol Physiol 2015;308:L130-L140

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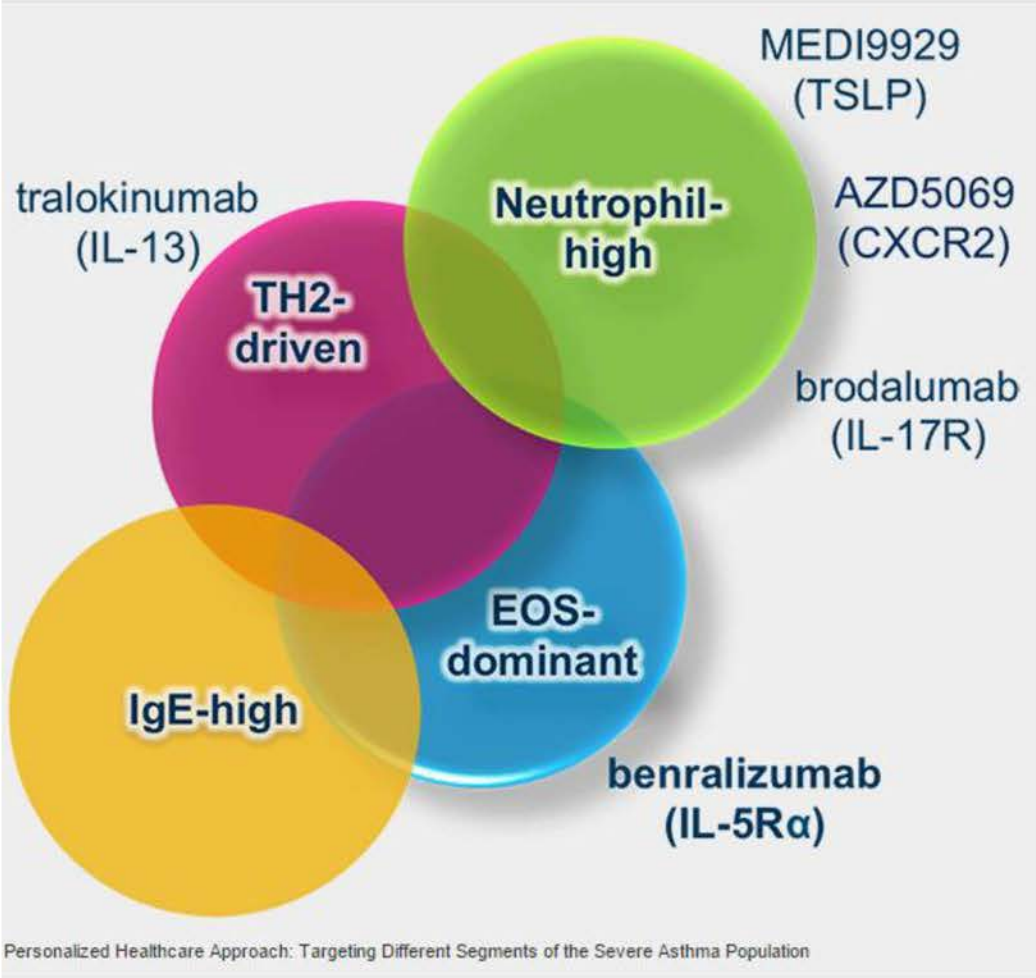
AMERICAN JOURNAL OF PHYSIOLOGY
Lung Cellular and Molecular Physiology

Medimmune/AZ Targeting Severe Asthma



Personalized Healthcare Approach: Targeting Different Segments of the Severe Asthma Population

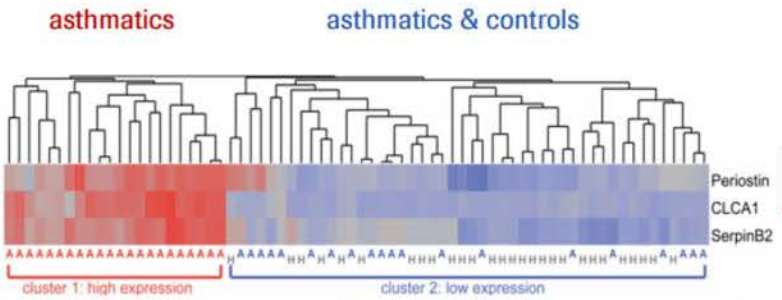
http://biotuesdays.com/2014/01/07/in-conversation-with-bing-yao/

Rationale for Targeting IL-13

Asthma: Identification of asthma patients likely to benefit from anti-IL-13 (Lebrikizumab) therapy

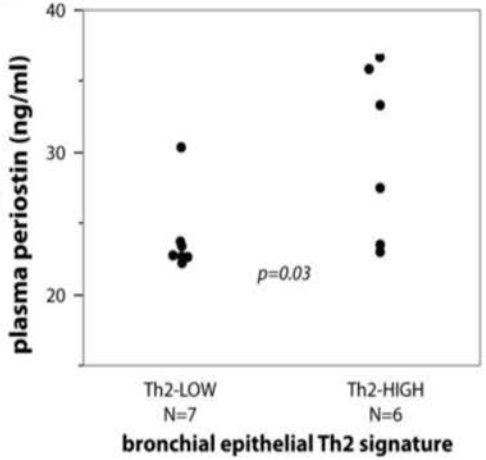
Roche

IL13 induced genes in lung epithelial brushings



Responsive to α-IL-13? | **Non-responsive to α-IL-13?**

Blood periostin levels in asthmatics



- **Peripheral blood periostin may serve as a *non-invasive* surrogate for IL-13 related asthma**
- **A predictive diagnostic marker (periostin) may predict improved clinical responses to Lebrikizumab**

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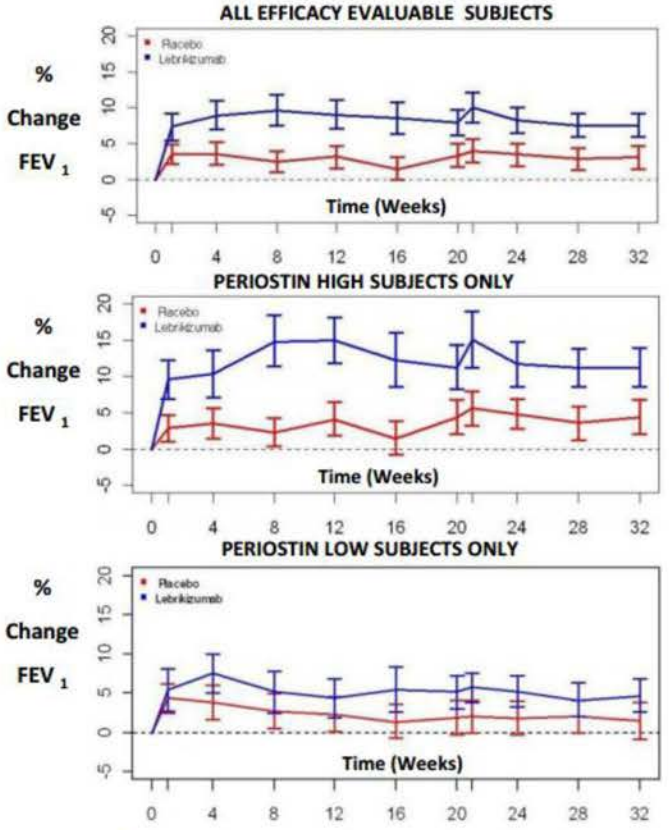
Internal data

Rationale for Targeting IL-13

Asthma: Relative change in FEV1 from baseline in asthma patients treated with Lebrikizumab



	Relative Mean FEV1 change at week 12		
	Total ITT population	Periostin High	Periostin Low
Placebo	4.3%	5.8%	3.5%
Lebrikizumab	9.8%	14.0%	5.1%
Difference	5.5% (p=0.02)	8.2% (p=0.03)	1.6% (p=0.61)

Periostin assay

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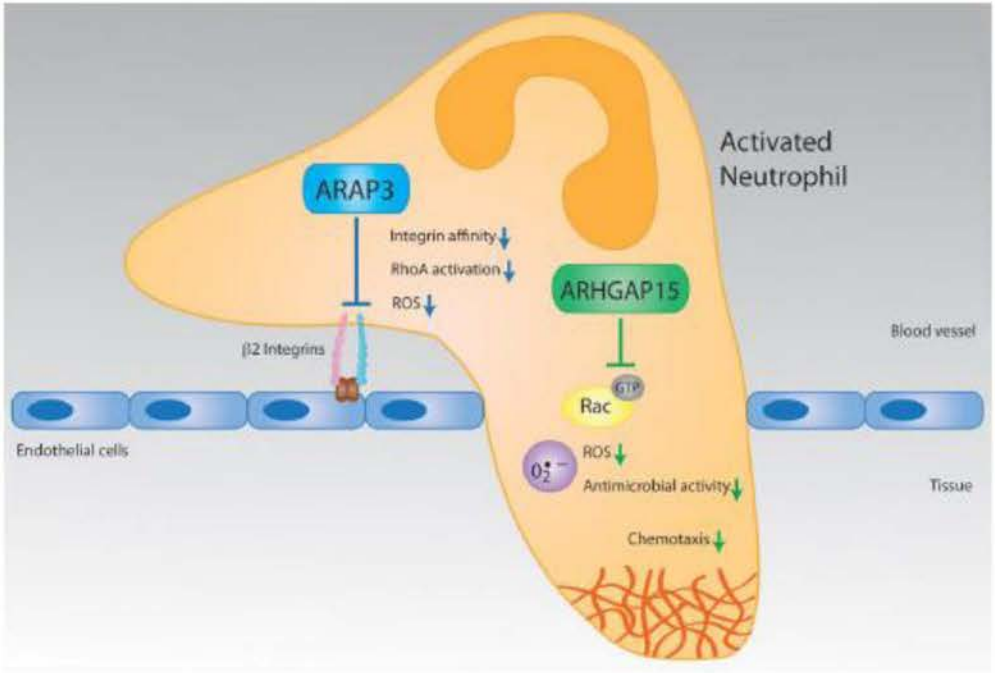
Corren et al. NEJM, 2011

Project Example:GTPases in Targeting Neutrophils

- ARHGAP15 knockout affects RAC1
- Neutrophils in ARGAP15 -/- show decreased circulating neutrophil and macrophages
  - Increased motility
  - Increased phagocytosis
  - Increased ROS generation
  - Increased Bacterial Killing
- Animals were protected from induced sepsis
  - Reduced secretion of cytokines



These Studies Suggest That There May Be Utility in Targeting Specific GTPases

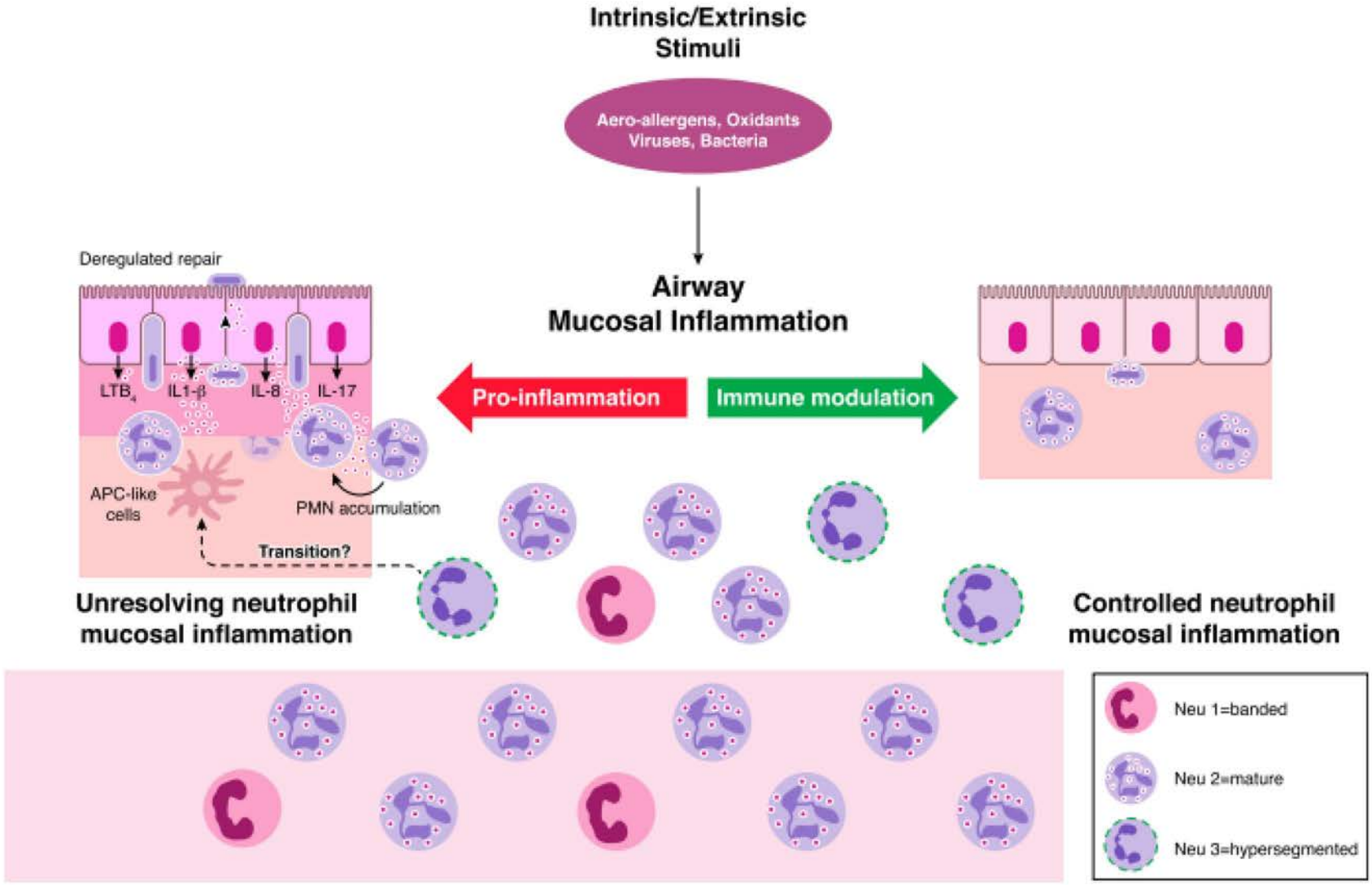


Figure 1. Schematic representation of potential phenotype switching of neutrophils during airway mucosal inflammation in severe asthma. Under homeostatic conditions, neutrophils are present in the circulation predominantly in a mature (neu-2) phenotype. Upon immunologic stress, 2 additional phenotypes mobilize in large numbers: banded (neu-1) and hypersegmented cells (neu-3). In contrast, in neutrophilic asthma, particularly during an exacerbation, there may be a shift in the phenotypes resulting in differential neutrophils homing toward the airway tissue as a consequence of epithelial-derived mediators (e.g., LTB_4, IL-8, IL-1β, IL-17A). These neutrophil-active factors could not only extend neutrophil life span to increase their proinflammatory potential but also affect their potential transformation into other repopulating cells, such as neutrophil-APC hybrid cells that may interact with T cells to precipitate mucosal neutrophilic inflammation.

Neutrophils in Disease

- Strategies to inhibit RAC may have significant potential in Neutrophil mediated diseases
- Significant market potential but highly competitive markets
  - High throughput screening for small molecules
    - Cell based assays to further clarify RAC inhibition on Neutrophil activities compared to other products in development
    - High unmet need in many indications
  - Potential for inhaled formulation for COPD/Asthma
    - COPD and Asthma preclinical studies
    - Need to identify KOL's for asthma in Canada
    - Small molecule approach may allow for decreased costs compared to biological therapy

Role of Neutrophils in Inflammatory Lung Disorders

- Neutrophils have been found to have a role in various inflammatory pulmonary disorders including Asthma, COPD, Cystic Fibrosis, and Acute Lung Injury
- Due to heterogeneous nature of these disorders, researchers have looked to identify different disease phenotypes including the role of neutrophils
- Researchers have recently applied concepts from oncology in order to target subsets of patients in order to improve effectiveness in these difficult to treat populations
  - Anti IL-5 for eosinophilic, Anti IL-13 for TH2 Asthma

Role of Neutrophils in Asthma

- Neutrophils are commonly found in the sputum of asthmatics, especially in severe asthma
  - The number of neutrophils has been found to be correlated with the severity of the disease
  - Patients with high levels of neutrophils have been shown to be resistant to inhaled corticosteroid therapy
    - Eosinophilic (Mild/Moderate) asthma responds better to inhaled corticosteroid therapy
    - Recent data from GSK for their anti IL-5 antibody for eosinophilic subtype is a good example of the benefit of testing Asthma subtypes

Potential Benefits of RAC Inhibition

- Various MOA's have targeted Neutrophil activity with limited success
- RAC2 Inhibition may have advantages compared to other MOA's
  - GTPase affects many functions of neutrophil function including signaling to other cells, chemotaxis, and reactive oxygen release
  - Other strategies such as IL-8 Inh may only affect chemotaxis which may not sufficient to impact disease progression

Neutrophil Inhibitors Potential Inflammatory Lung Disease Patient Populations in Major Markets

Disease	Big 7 Market Prevalence (US, EU5, JPN)	WW Pharma Sales	Notes
Asthma*	67M	$16B	Severe Neutrophilic Asthma is estimated to be ~5 to 10% or ~3 to 7M
COPD*	41M	$10.5B	Unclear what % would be neutrophilic
Cystic Fibrosis	80K WW	$1.1B	New Vertex drug will Increase Market

*It may be interesting to look at Bronchitis (GSK doing this with Mepolizumab) mediated by Neutrophils as a separate sub-population

Deal-making in Pulmonary Inflammation

Partners	Program	Upfront	Milestones	Notes
Funxional Therapeutics/ Boehringer Ingelheim (2012)	FX125L, Somatotaxin program	?	?	Oral QD dosing Phase II ready
Amgen/Astra Zeneca (2012)	Multiple (5) Clinial Molecules	$50M	>$500M	Pulmonary Inflammation & Other Disorders Anti IL-17 is late stage
Reata/Abbott Labs (2011)	Antioxidant Inflammation Modulators	?	$400M	2nd partnership between companies NrF2 Activation
Portola/Biogen Idec (2011)	Oral Syk Inh.	$45M	$553.5M	Asthma, Lupus, Cancers, RA
University of Michigan/Mediummune (2011)	Multiple	?	?	3 Yr Preclinical & Translational Med Agreement

*Note there are many more deals in Inflammation Which May Target Pulmonary Disorders but therapeutic area was not disclosed (Medtrack)

Conclusions

- Market assessment of new opportunities is driven by both scientific and business information
- At CDRD we look at market data from providers such as Evaluate Pharma (pipeline, market data) and Recap (deals data) along with presentations from pharmaceutical and biotech players in the space and solicit feedback from our Innovation partners
- Freedom to operate analysis is also critical
- Health economics important but difficult to assess at the early stage of a program

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