Using biomarkers to enable drug development for asthma

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31 August, 2011

Four reasons why a drug candidate might fail

1) Wrong target
   - hypothesized target/pathway not a critital node in disease pathogenesis
   - safety issues associated with target

2) Wrong molecule
   - insufficient affinity/avidity; off-target effects
   - poor PK/tissue penetration/inadequate dosing

3) Wrong outcomes
   - clinical outcome measure not related to biology of target
   - clinical outcome measure not relevant in trial population

4) Wrong patients
   - patients not properly stratified according to molecular, pathophysiological, or clinical heterogeneity
   - trials underpowered to detect an effect in the right subset

Definitions

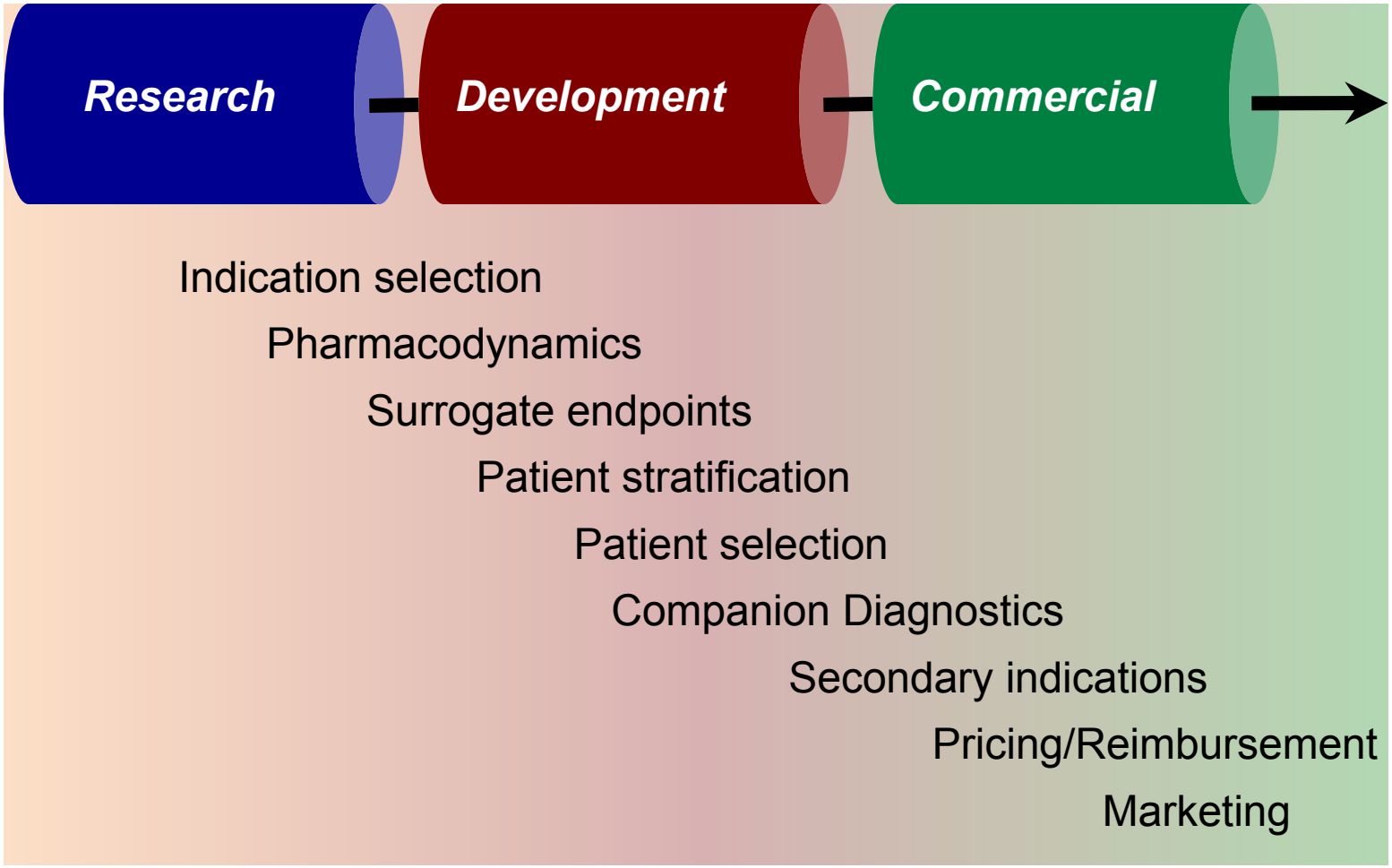
How do biomarkers help us help patients?
"Targeted therapy" means *selecting the right treatment for the right patient*

Biomarker: A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention.

Diagnostic: A biomarker that has applicability in clinical use or patient management (*e.g.* to identify a sub-population of patients who would benefit most from a drug or suffer adverse events from a drug).

Biomarker Type	Definition
Screening	Discriminates "healthy" from beginning "disease" state, preferably in the asymptomatic phase.
Prognostic	Predicts likely disease course once disease status is established, influences aggressiveness of intervention.
Predictive	Predicts likely efficacy/safety response to drug prior to starting treatment.
Pharmacodynamic	Confirms drug activity, and enables optimization of dose and administration schedule.

Biomarkers can impact all stages of drug development

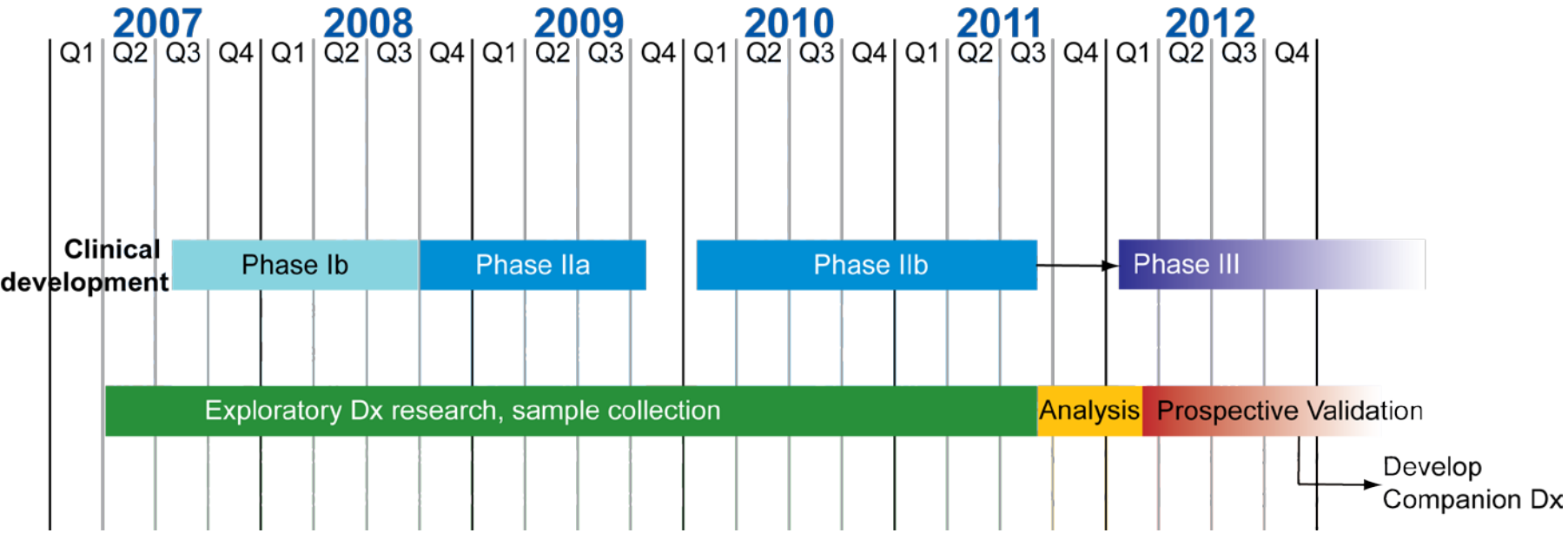


How do we approach biomarker development?

- Understand disease heterogeneity and stratify patients
  - human autoimmune/inflammatory diseases are heterogeneous
  - disease-focused, not treatment-focused exploratory approach
  - match patient subsets with best-fit treatment options

- Use biomarkers to improve clinical trial outcomes
  - treat disease subtypes most likely to benefit from targeted therapy
  - optimize dose selection
  - measure surrogates of pathophysiological effects
  - identify and treat patients earlier in the course of their disease
  - improve response rate & increase chances of trial success
  - maximize therapeutic value in a competitive market

Retrospective diagnostic development

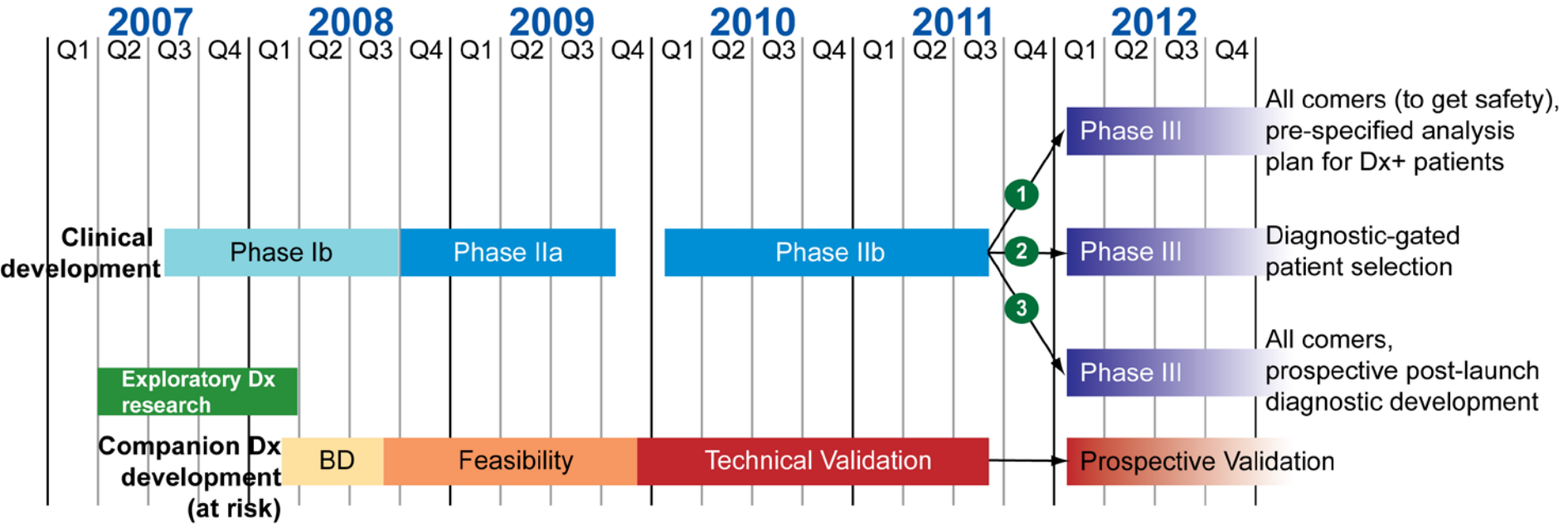


Retrospective approach: use samples and data from clinical trials to identify subsets enriched for response.

Problems:

- does not enable pre-specified patient selection in pivotal trials
- cannot launch drug with a companion diagnostic

At-risk Companion Diagnostic development



Phase II retrospective analysis outcomes:

1. Predictive diagnostic works, but significantly impacts PhIII recruitment
2. Predictive diagnostic works, has minimal patient selection impact
3. Predictive diagnostic doesn't work

At-risk approach: develop markers/assays based on biology/MOA concurrent with clinical trials

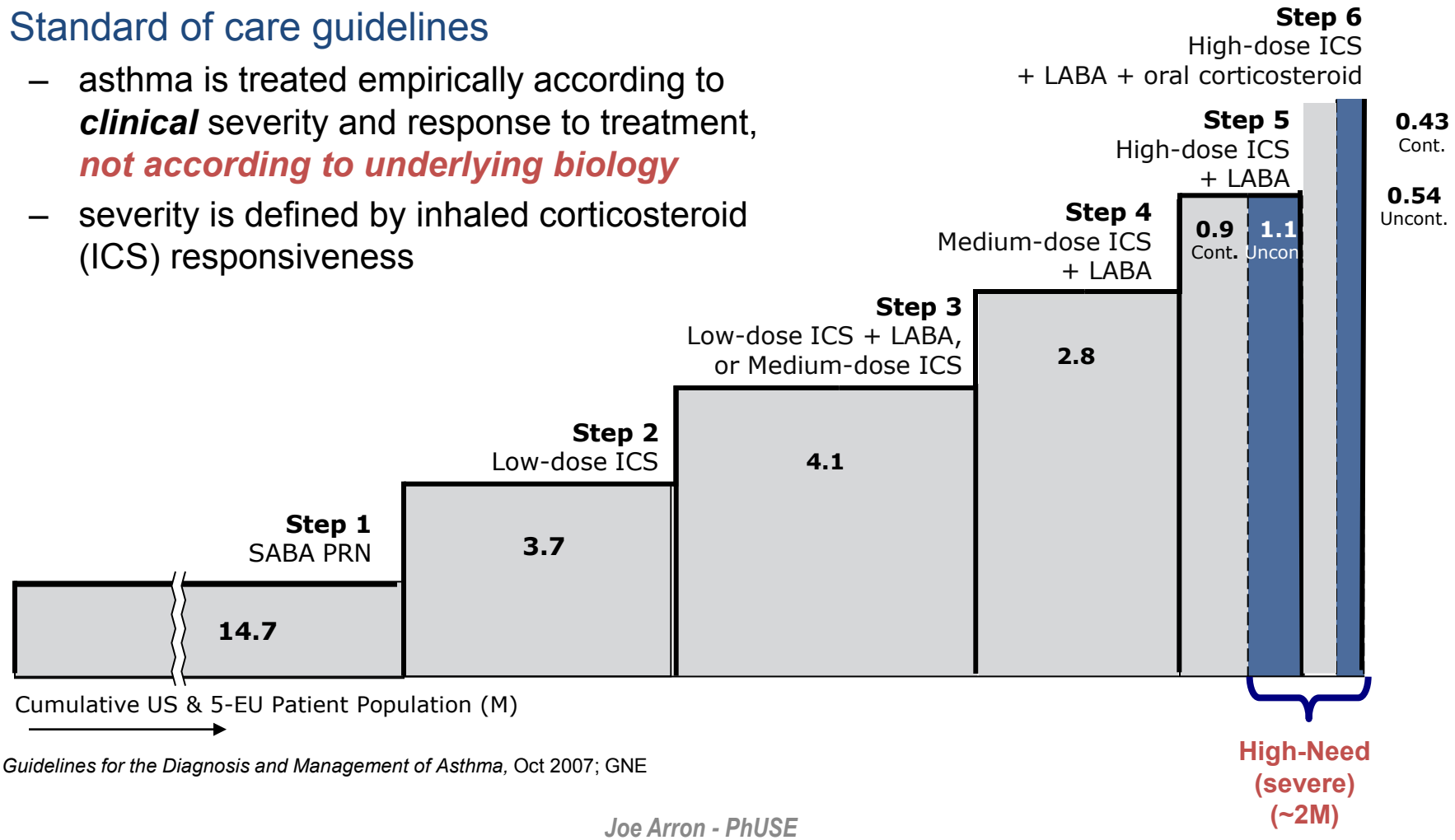
- increased up-front expenses
- risk that marker (or therapeutic) won't work as planned

***Lesson learned**: If biomarkers are to impact pivotal clinical trial outcomes, we may need to develop companion Dx at-risk*

Asthma is treated empirically

- Definition
  - **ASTHMA:** a syndrome of loosely affiliated pathological processes resulting in reversible airway obstruction and hyperreactivity

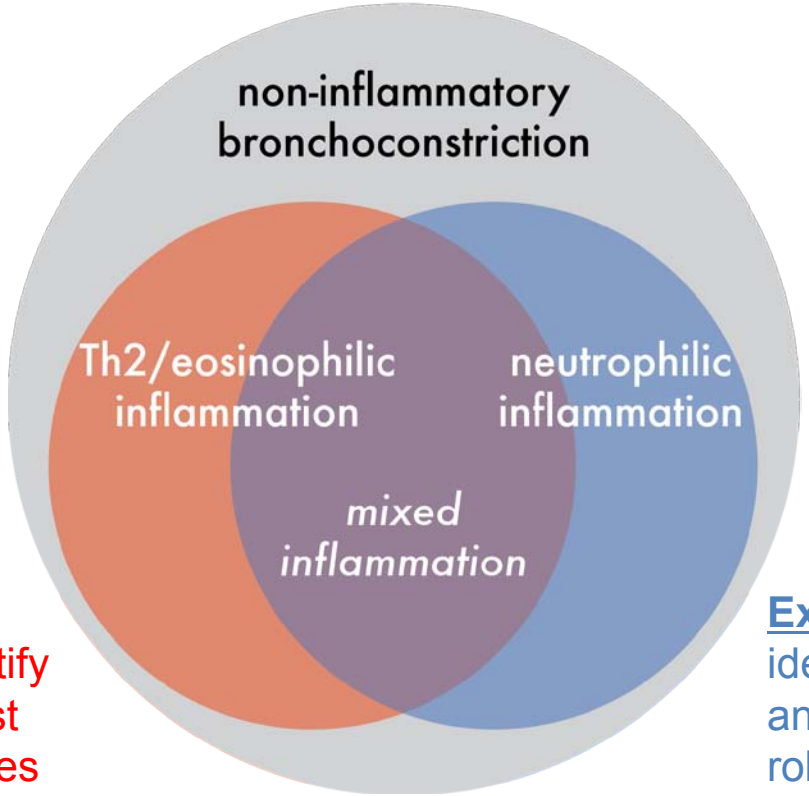
- Standard of care guidelines
  - asthma is treated empirically according to ***clinical*** severity and response to treatment, ***not according to underlying biology***
  - severity is defined by inhaled corticosteroid (ICS) responsiveness



NHLBI *Guidelines for the Diagnosis and Management of Asthma,* Oct 2007; GNE

Asthma heterogeneity is a challenge for drug development

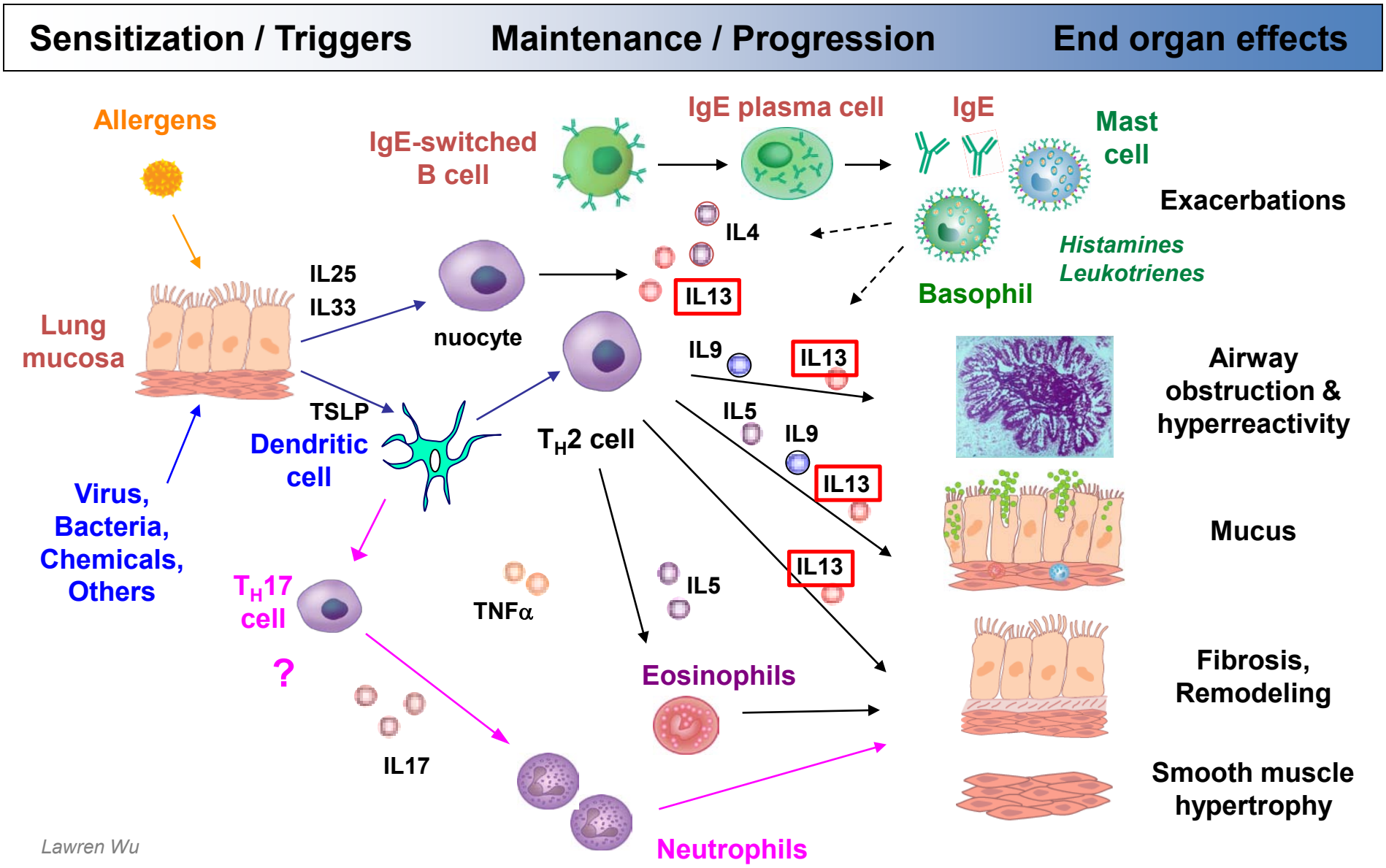
etiologic subtypes of severe asthma



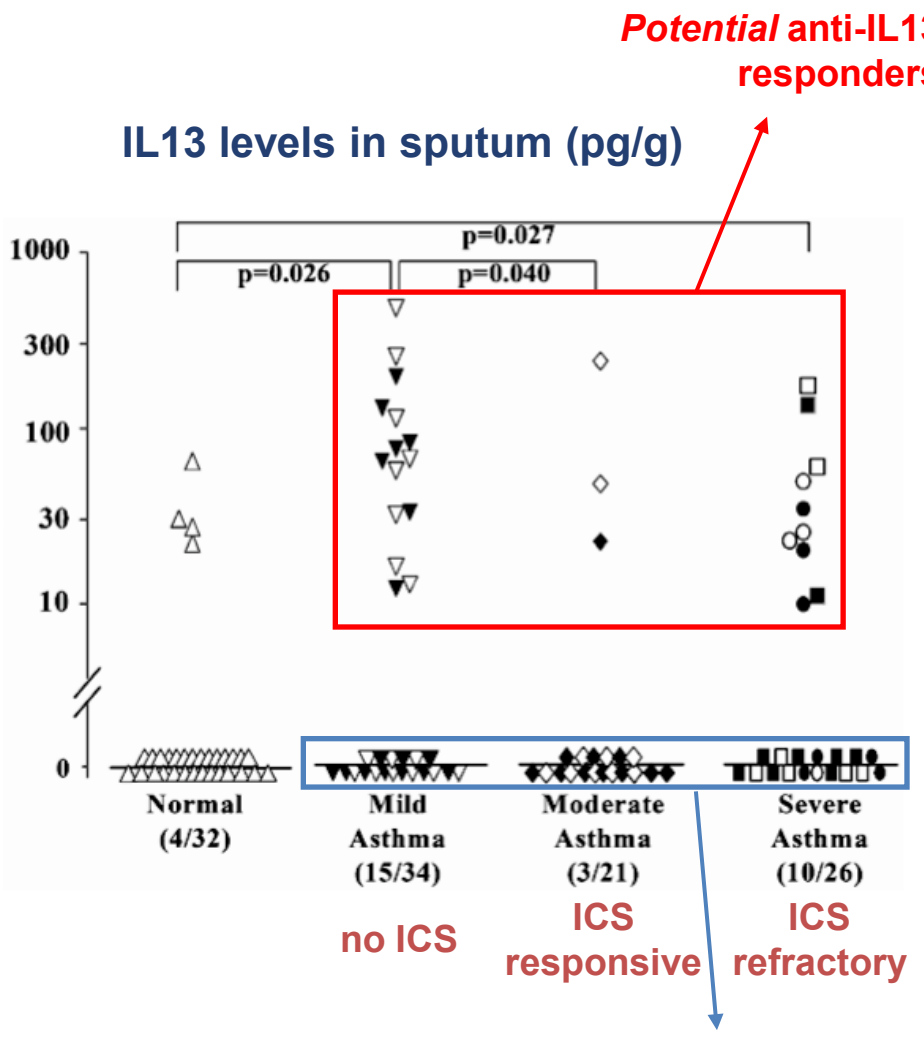
Support the pipeline
discover biomarkers to identify and monitor asthmatics most likely to benefit from therapies targeting Th2 inflammation

Expand the pipeline
identify, pathways, targets, and biomarkers that may play roles in non-Th2 asthma

Multiple mediators contribute to asthmatic airway inflammation



Elevated airway IL13 in subsets of asthma



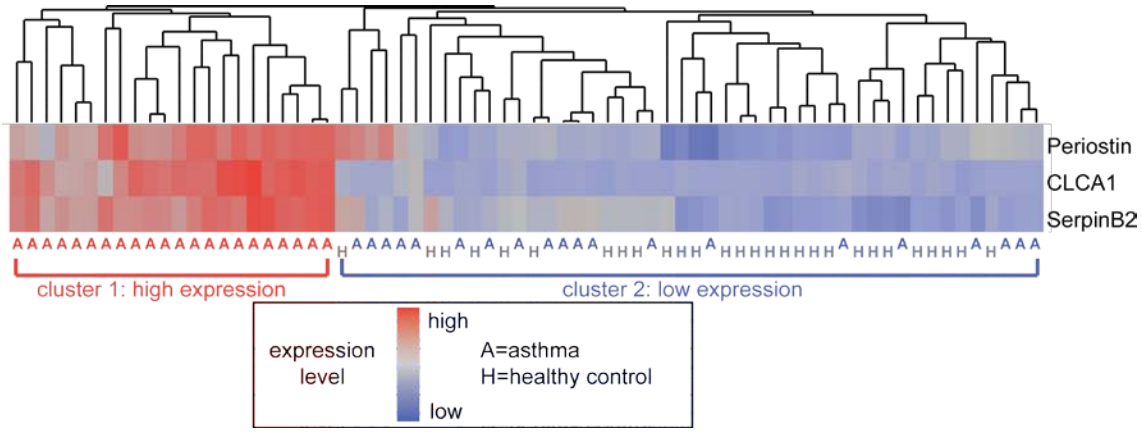
Saha SK et al, *JACI* **121**:685-91 (2008)

- Airway cytokine expression is heterogeneous in asthmatics
- Systemic IL13 is difficult to measure and does not correlate to airway inflammation
  - Direct airway sampling is impractical in large clinical trials
- *Does IL13 in the airways influence the expression of other genes that may encode systemic biomarkers?*
  - If so, how can we identify these markers?

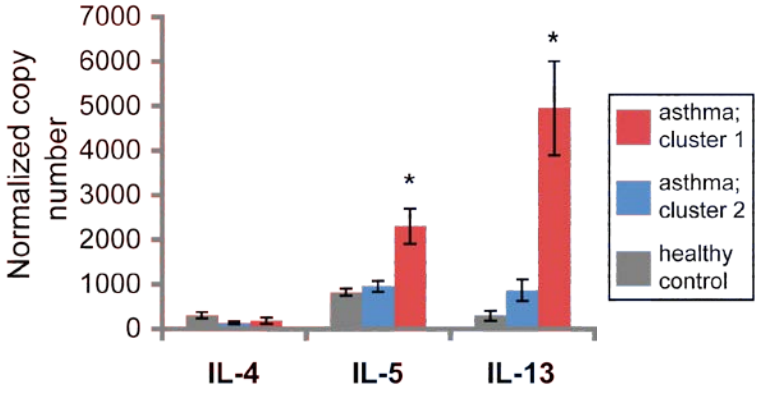
Two groups of asthmatics are defined by a bronchial epithelial gene signature

IL-13 responsive gene signature in bronchial epithelium

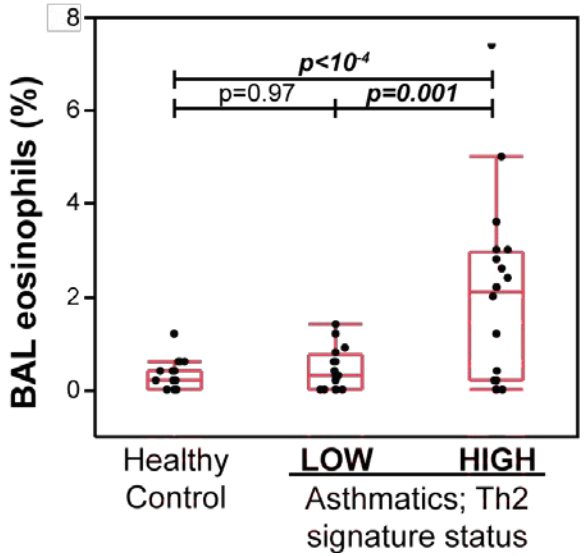
asthmatics | asthmatics & controls



Th2 cytokine expression in bronchial biopsies



Airway eosinophilia



IL13 "HIGH" and "LOW" asthmatics are distinguished by

- eosinophilic airway inflammation
- subepithelial fibrosis
- mucus composition

What about response to therapy?

Woodruff PG et al, *AJRCCM* **180**:388 (2009)

Biomarker discovery strategy for anti-IL13

- ***Hypothesis***

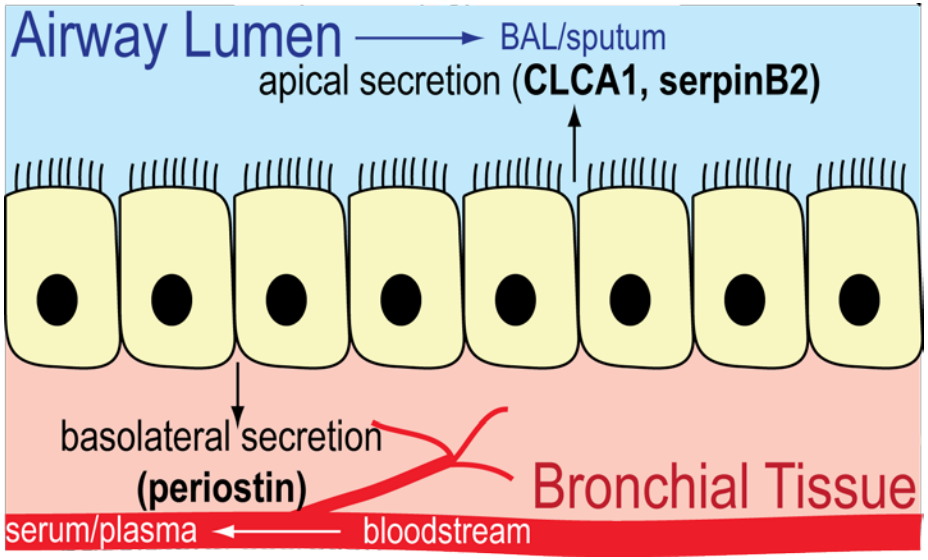
  asthmatics with eosinophilic airway inflammation are most likely to experience clinical benefit from IL13 blockade

- ***Are there systemic biomarkers that noninvasively identify these subsets?***

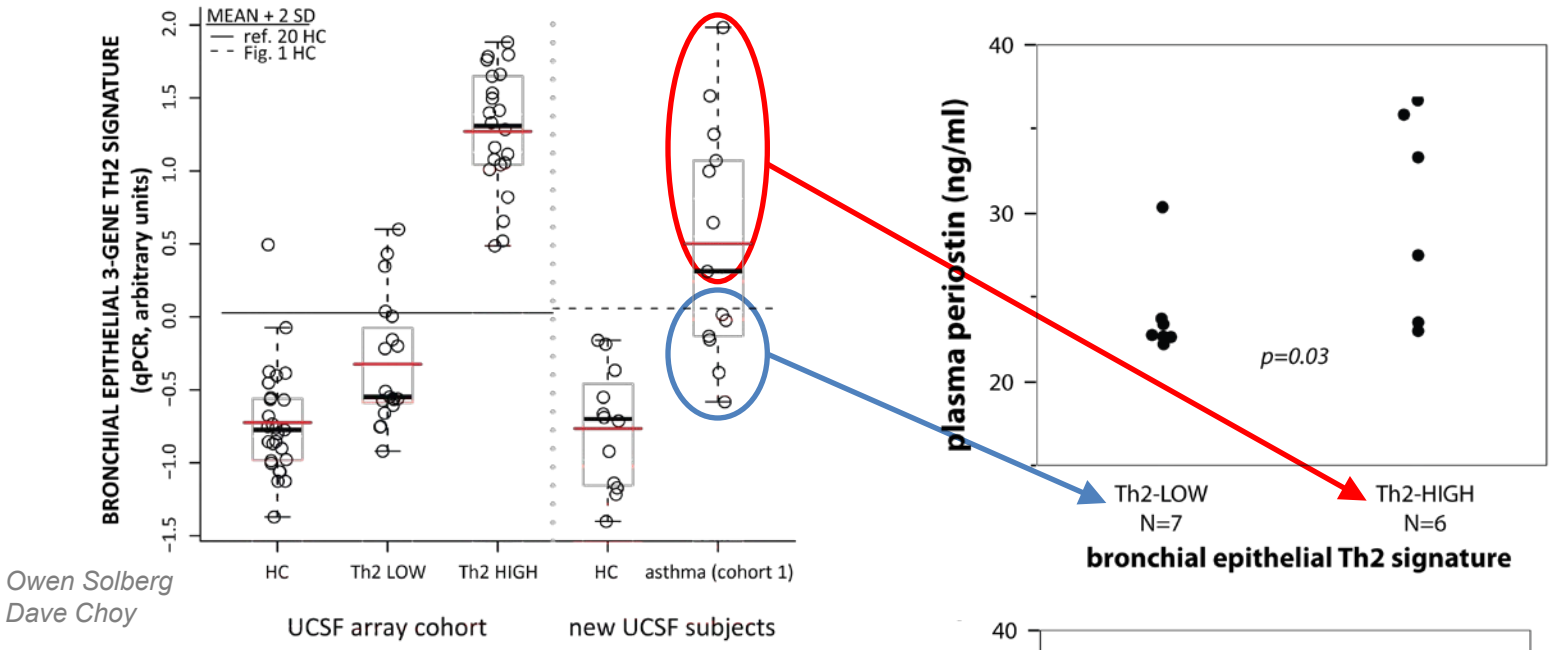
- Desired features of systemic biomarkers of eosinophilic airway inflammation
  - Detectable in blood of asthmatics
  - Accurately reflect airway inflammation
  - Mechanistically linked to IL13
  - Robust, reproducible assays available

Experimental approach

identify genes co-regulated with the IL13 signature that encode soluble/secreted proteins detectable in blood



Systemic periostin levels differentiate mild-moderate asthmatics on the basis of airway IL13 signature and eosinophilia



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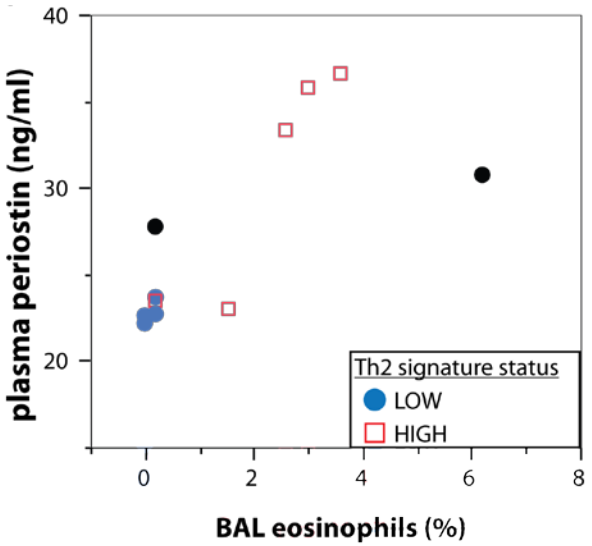
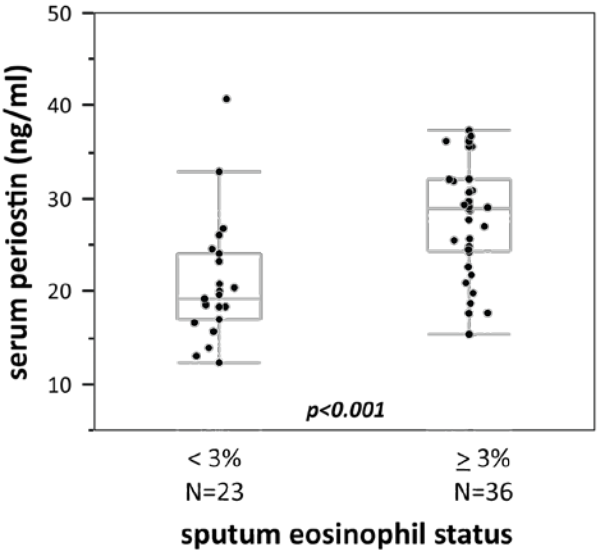
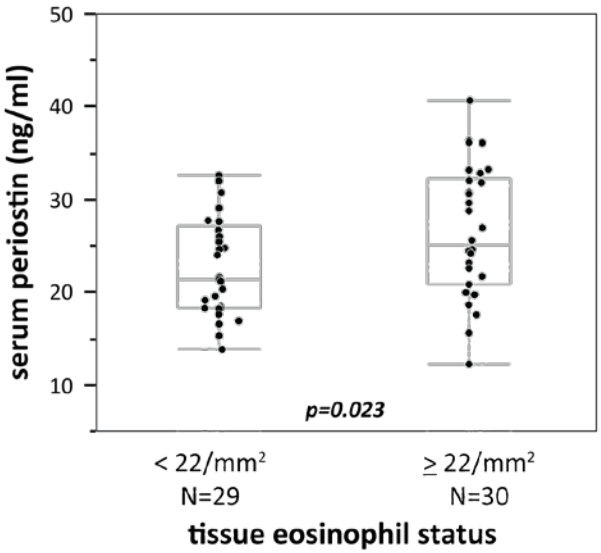


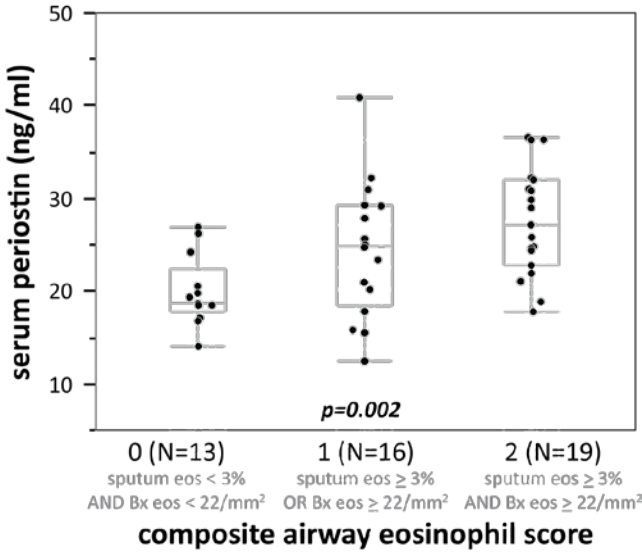
- Replicated previous finding of epithelial IL13 gene signature
- IL13-HIGH asthmatics have higher blood periostin than IL13-LOW asthmatics
- Eosinophilic asthmatics are IL13-HIGH and have elevated blood periostin levels

Serum periostin is elevated in severe asthmatics on ICS with residual eosinophilic airway inflammation

BOBCAT cohort





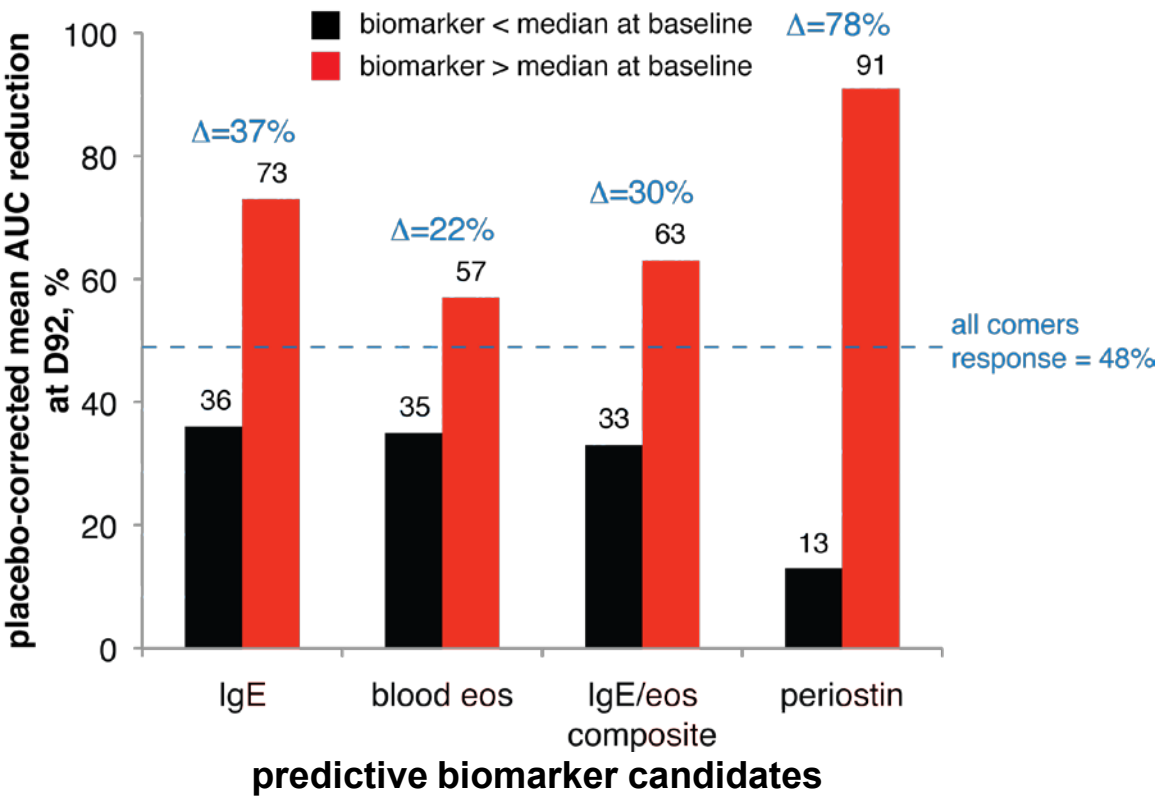


Airway eosinophil cutoffs pre-specified from literature:

Sputum 3% Haldar et al, *NEJM* **360:**973 (2009); Green et al, *Lancet* **360:**1715 (2002); many others

Tissue (total biopsy area) 22/mm^2 Miranda et al, *JACI* **113:**101 (2004); Silkoff et al, *JACI* **116:**1249 (2005)

Lebrikizumab Phase 2a (allergen challenge): Baseline biomarkers predict increased clinical benefit

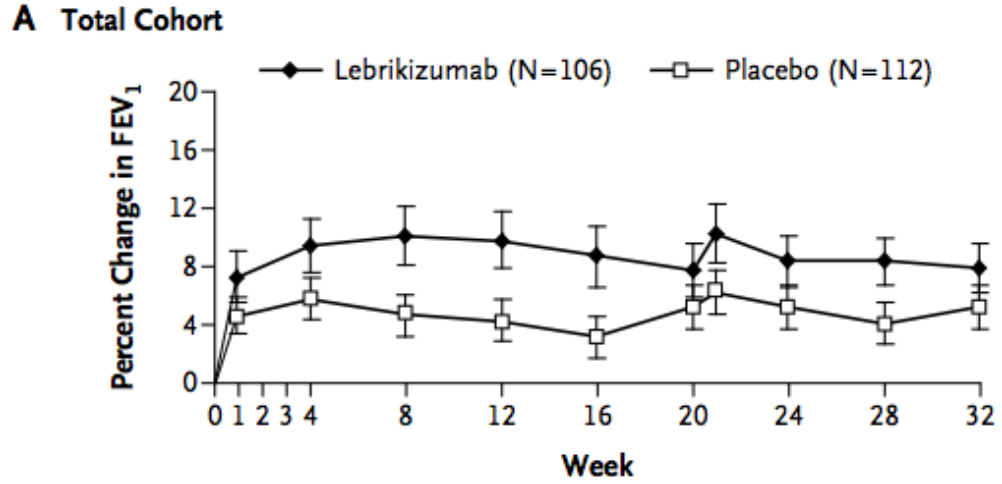


Zheng Su
Rich Erickson

Caveats

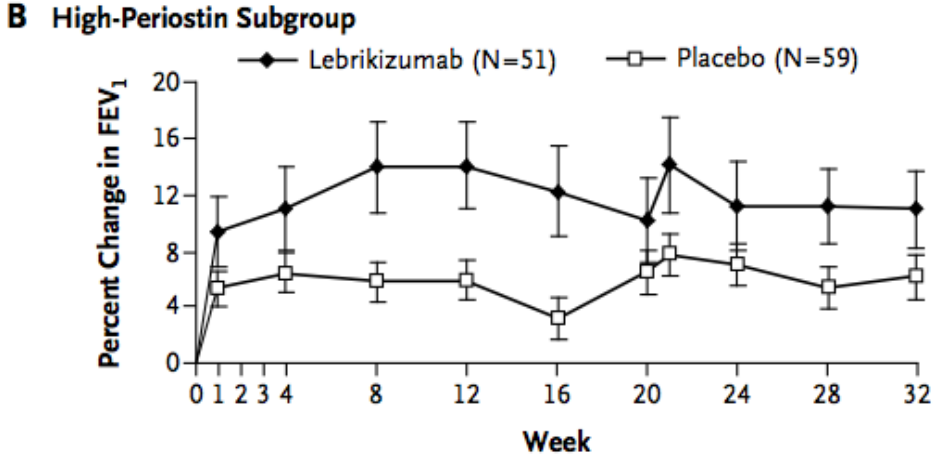
- Due to small N, median values selected to dichotomize groups (5-8 active subjects/group)
- Due to small N, outliers can skew results
- Unclear whether these cutoffs will translate to more severe asthmatics
- ***Unclear whether these markers will predict benefit for clinical endpoints in target population (chronic lung function, exacerbation reduction)***

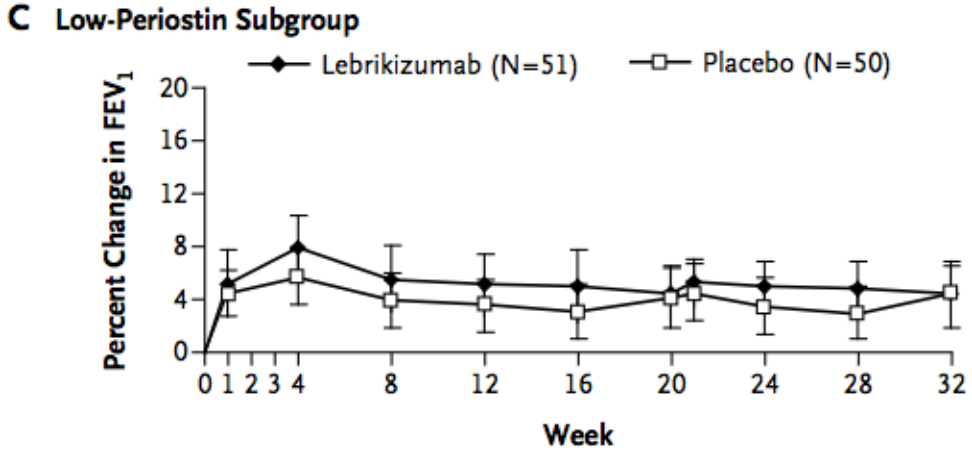
Lebrikizumab Phase 2b ("MILLY"): Efficacy based on periostin status



Placebo-adjusted effects on lung function

Group*	ΔFEV1, 12 weeks
All comers	5.5% (p=0.02)
Periostin HIGH	8.2% (p=0.03)
Periostin LOW	1.6% (0.61)





Corren et al. NEJM, 2011

Four reasons why lebrikizumab might succeed

1) Right target?
   - IL13 blockade appears to be well-tolerated and efficacious because...

2) Right molecule?
   - high affinity, long half-life, minimal off-target binding
   - dramatic effect on FeNO (airway PD marker of IL13 activity) and...

3) Right outcomes
   - substantial impact on lung function both in allergen challenge and chronically
   - dramatic reduction in severe exacerbations because...

4) Right patients
   - substantial differences between periostin-high and periostin-low patients

Let's hope for the best in phase III!

Acknowledgments

Arron lab (past and present)

Dave Choy
Jim Jia
Sanjay Chandriani
Matt Yocum
Stacy Miller

ITGR Biomarker Discovery

John Monroe, Tim Behrens,
Katie Bradley, Ward Ortmann,
Katrina Morshead
Mike Townsend, Mary Keir,
Marcel van der Brug, Rob Graham

Immunology Discovery

Lawren Wu
Flavius Martin
Harinder Singh
Andy Chan

Bioinformatics

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Alex Abbas
Robert Gentleman
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