Cutting edge developments: biomarker qualification as an indicator for clinical endpoints and their role in setting an optimal biologic dose

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Biomarker definition

- “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological response to a therapeutic intervention” (NIH Biomarkers Definitions Working Group, 2001 Clin. Pharmacol. Ther.)

- “a xenobiotically-induced variation in cellular or biochemical components or processes, structures, or functions that is measurable in a biological system” (National Academy of Science)

Qualification of biomarkers

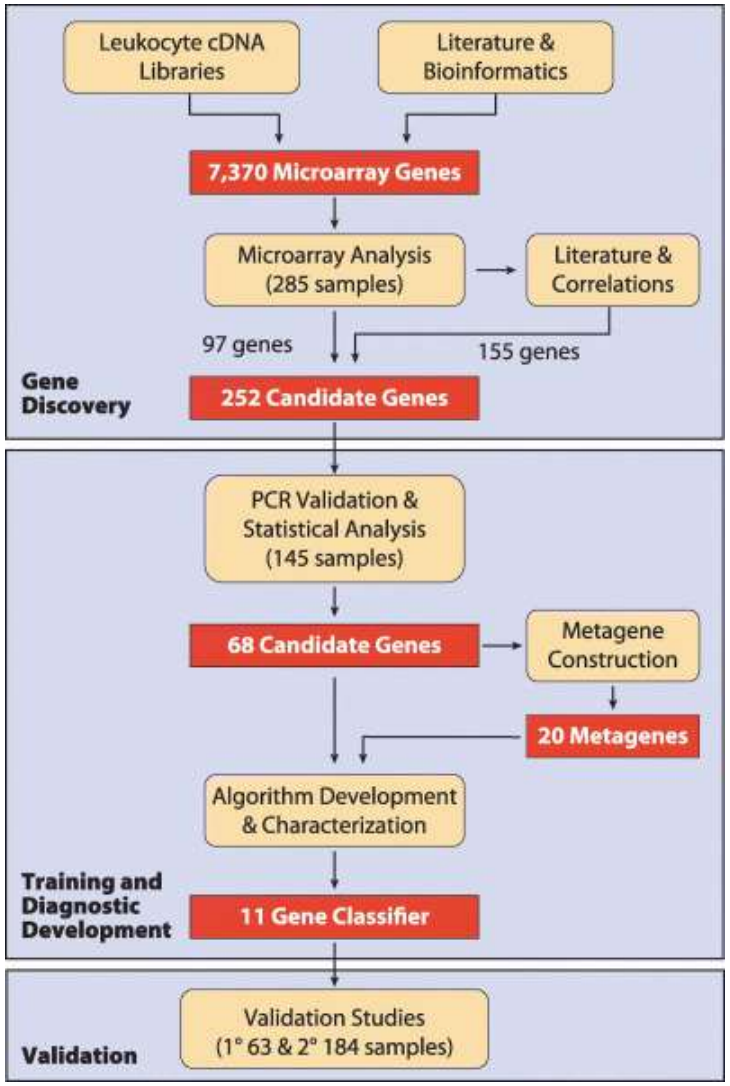
Biomarker	Description	Drug Development	Example
Exploratory	R&D tools	Hypothesis generation (key information)	Gene expression
Demonstration	Probable valid biomarkers	Supporting evidence	Adiponectin
Characterization	Known valid biomarkers	Decision making	Fasting plasma glucose
Surrogacy	Substitute for clinical endpoint	Registration	Hemoglobin A1C

All biomarker development and use should be guided by the principle of being linked to how they will be used ("fit-for-purpose"). *Clinical Pharmacology & Therapeutics (2007) 81, 104–107.*

Biomarkers in Phase I/II studies

- ***Qualification Process for Drug Development Tools*** ***October 2010 - FDA***
- Most pharmacodynamic biomarkers are used to guide drug development - clinical endpoints provide the basis for regulatory approval.
- Surrogate endpoints are a (very small) subset of pharmacodynamic biomarkers.
- Qualification of a biomarker as a surrogate endpoint is likely to occur much less often than qualification of biomarkers for other uses.
- ***Fit-for-purpose qualification is all that is needed in Phase I/II***

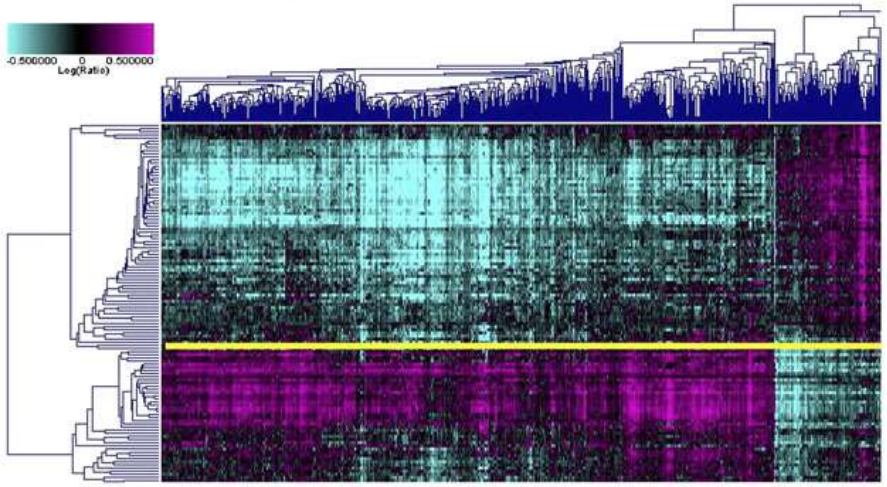
Non-invasive Discrimination of Rejection in Cardiac Allograft Recipients Using Gene Expression Profiling (FDA approved biomarker)



AlloMap® molecular expression testing

American Journal of Transplantation
Volume 6, Issue 1, pages 150-160, 13 DEC 2005 DOI: 10.1111/j.1600-6143.2005.01175.x

Gene expression profiling of human atherosclerotic plaque



Genes differentially expressed in plaque
Biological processes identified in plaque

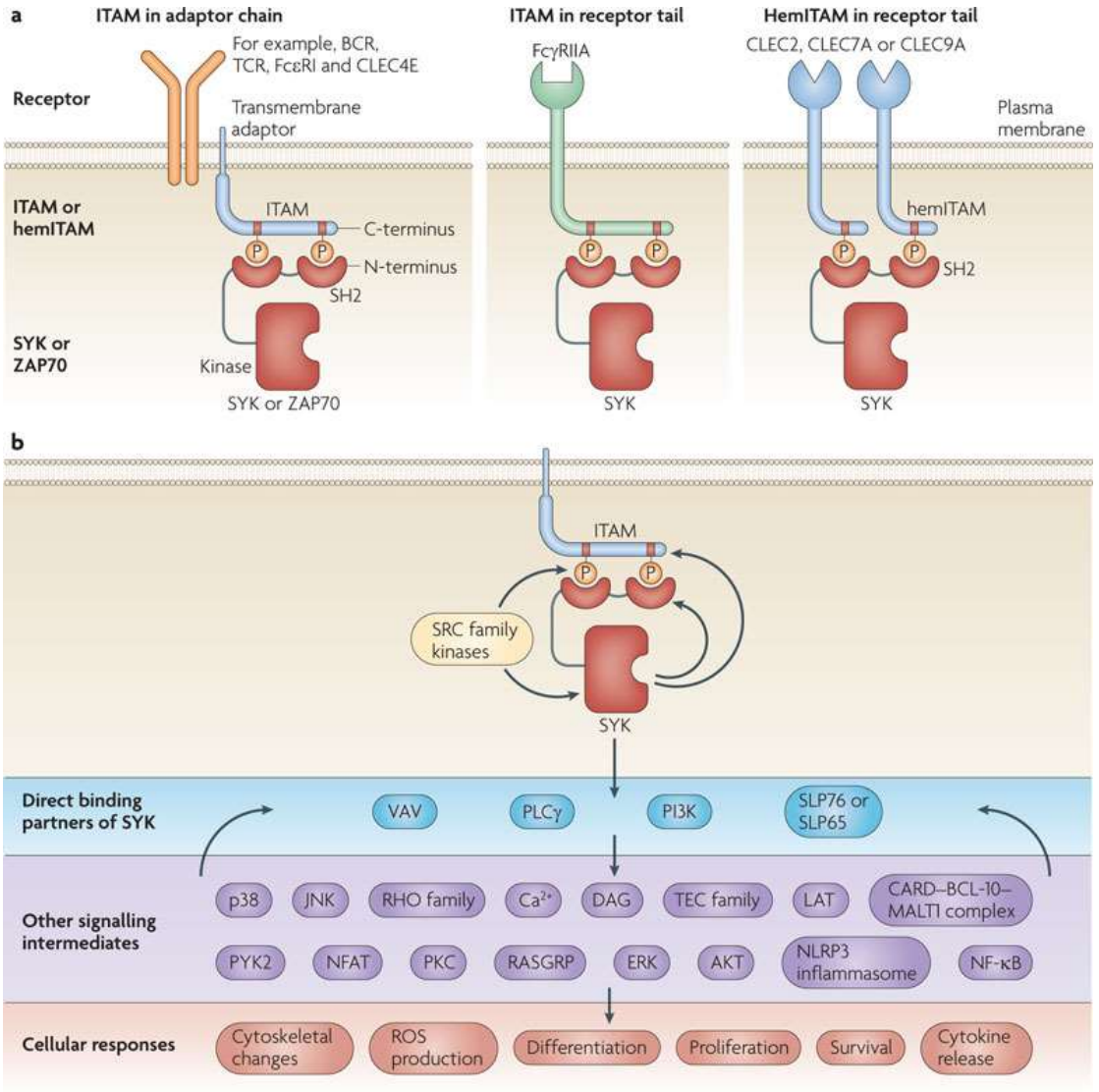
Plaque biomarkers

Validation of plaque biomarkers in experimental medicine clinical trials using known cholesterol lowering therapies

The AAPS Journal, 2011
DOI: 10.1208/s12248-011-9265-x

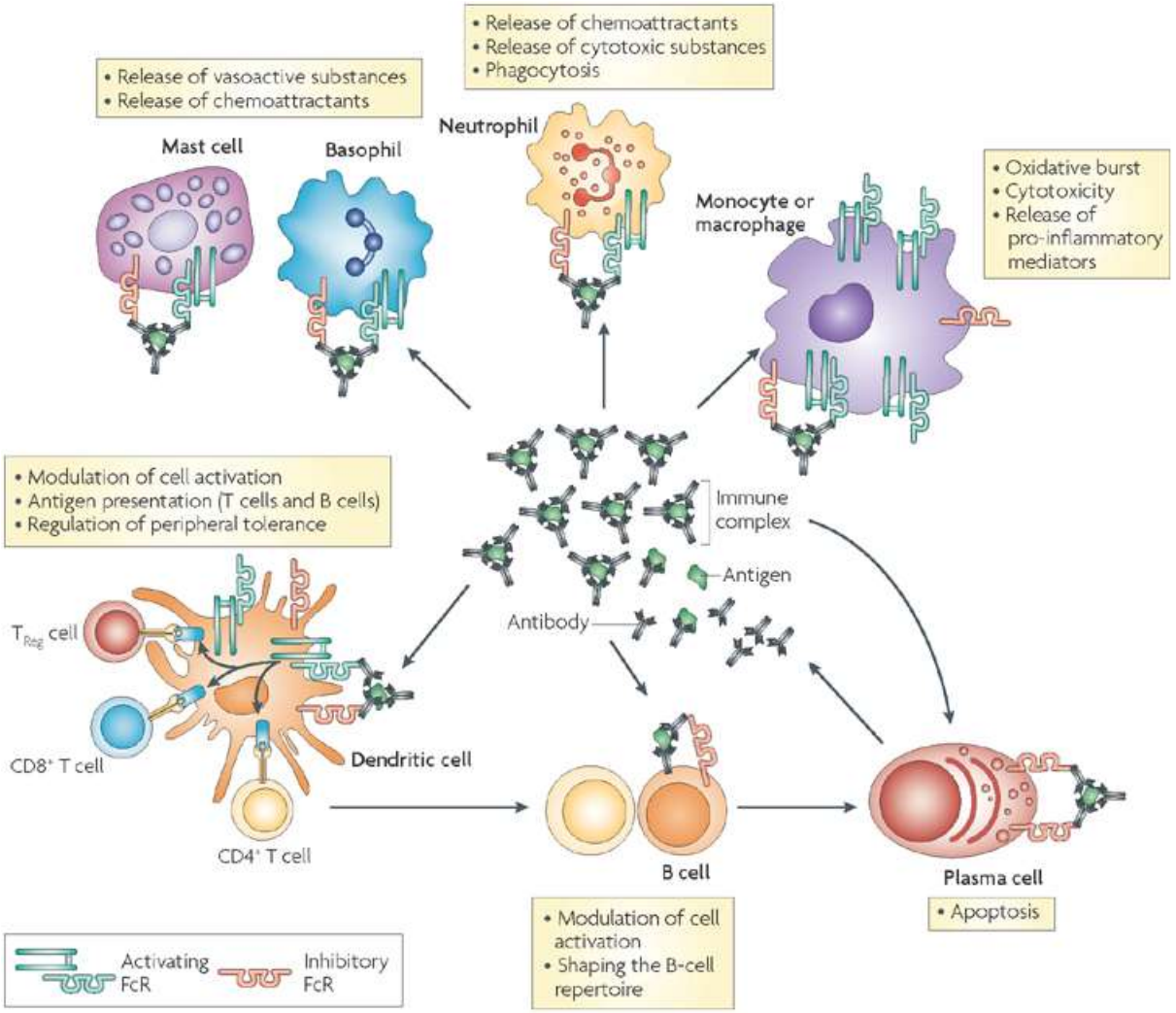
The primary endpoint of the trial, defined as a reduction in CD68 content as a surrogate for plaque inflammatory status was not observed…
Interestingly, clear pharmacodynamic markers of drug action could be identified…

Target molecule: Syk kinase (Fostamatinib)



Nature Reviews | Immunology

Syk kinase: activating Fc Receptors



Nature Reviews | Immunology

Fc epsilon RI: Syk kinase

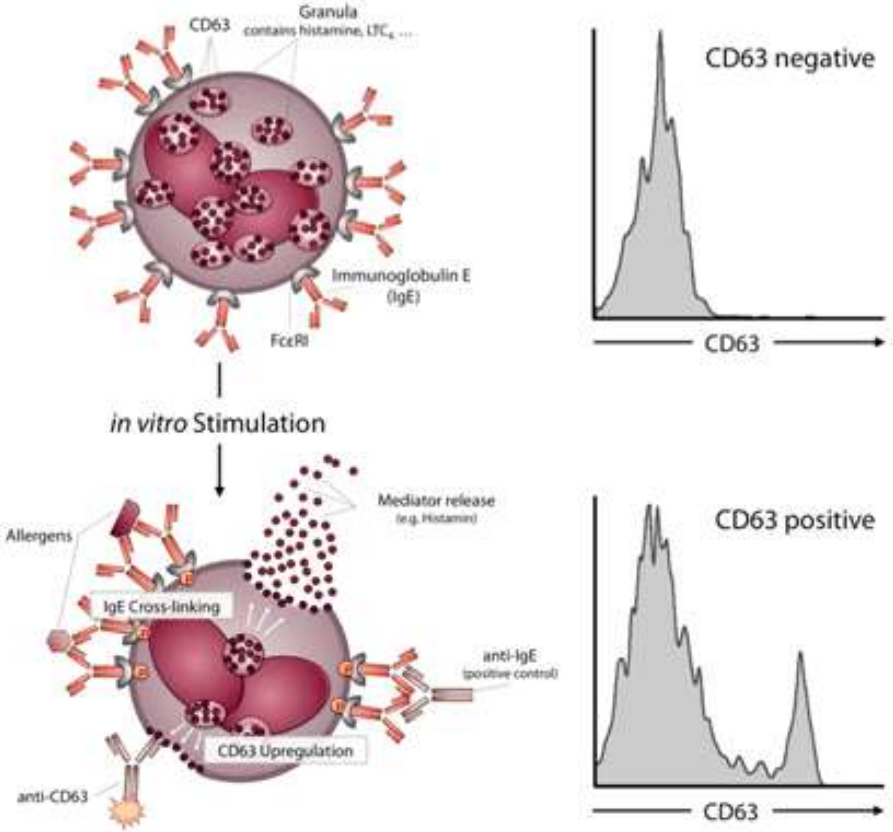
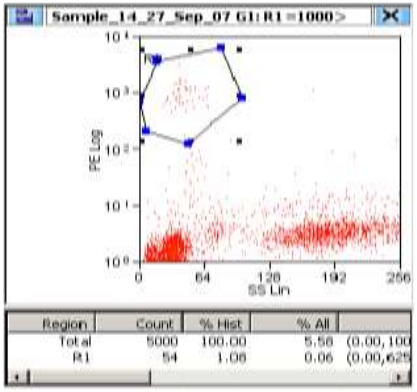


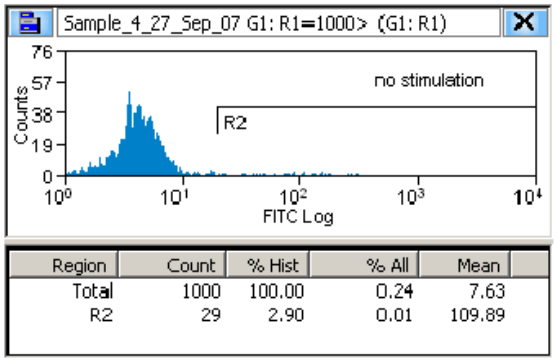
Figure 1. Principle of the basophil activation test.
Upon cross-linking of membrane-bound IgE, basophils upregulate the expression of specific activation markers such as CD63. These phenotypic alterations can be acquired by flow cytometry using monoclonal staining antibodies.

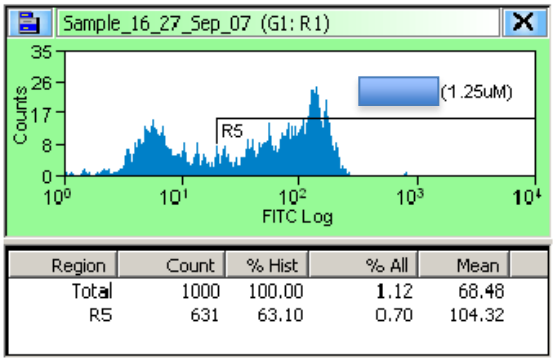
Inhibition of basophil activation by Syk inhibitor X

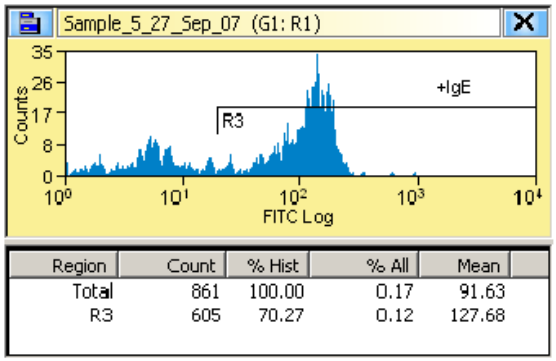
Looking at CD63 expression:

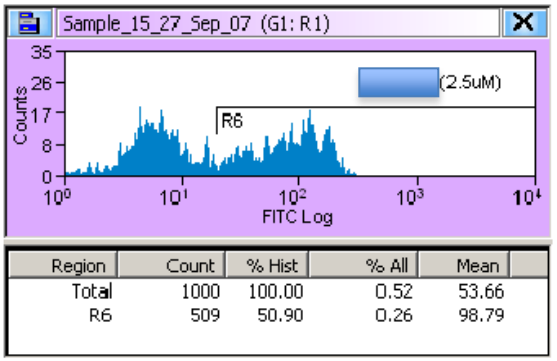
Gating on
IgE +ve cells

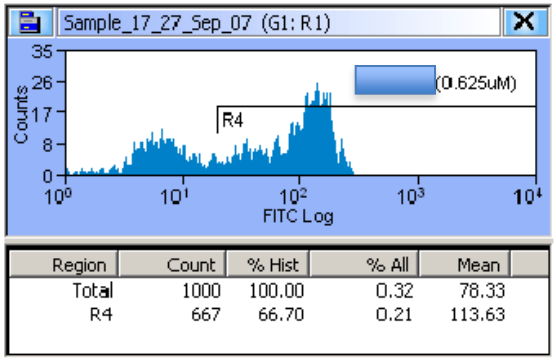


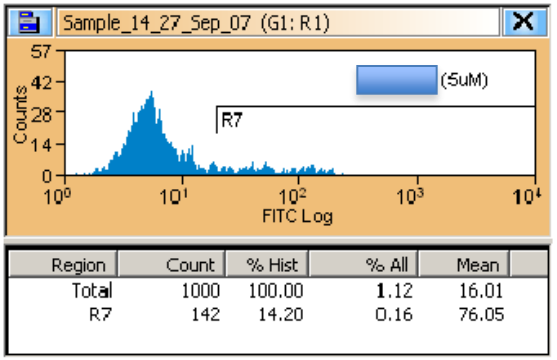




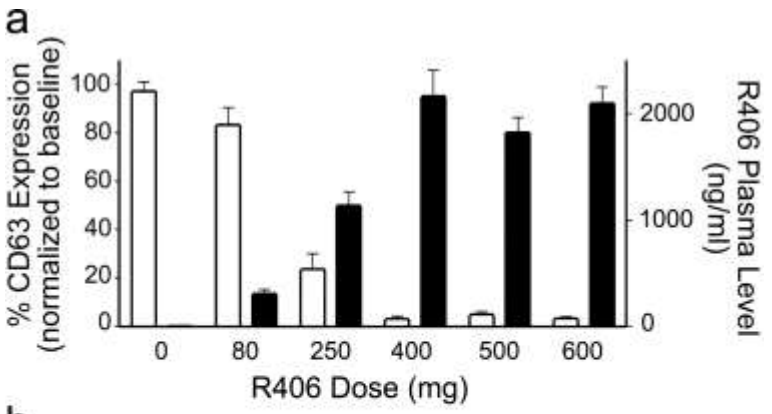


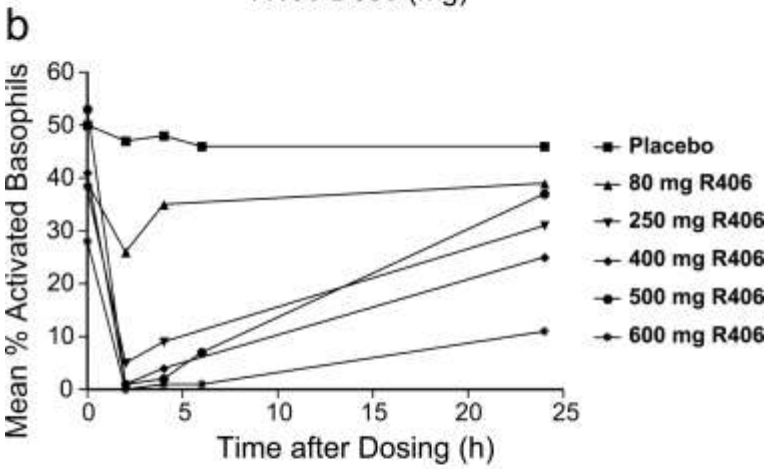


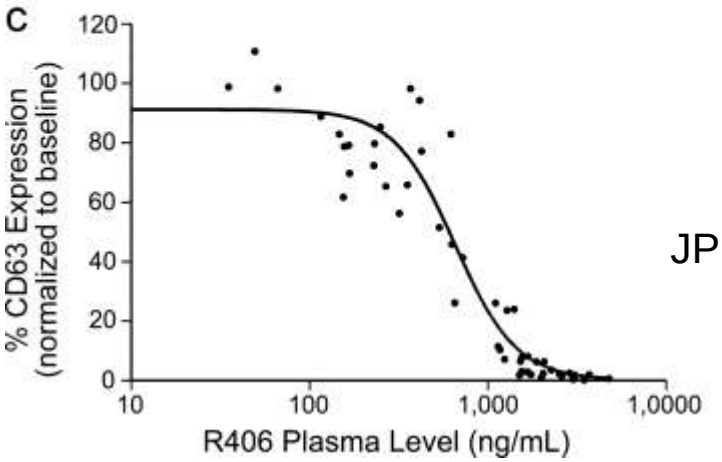




Relationship between pharmacodynamic effect and plasma concentration of R406 in humans (Fostamatinib)







JPET 319:998–1008, 2006

Biomarkers – safety & off target effects

- **Syk kinase inhibitor R406/R88/Fostamatinib**
- Beyond Syk, R406 inhibited Flt3, Jak, and Lck, which might be desirable
- A dose-dependent, reversible reduction of circulating CD14+ mononuclear cells (no effects on monocyte activation markers)
- No inhibition of platelet aggregation induced by collagen (via glycoprotein VI) or ADP
- Neutrophil/monocyte phagocytosis, oxidative burst were not affected

Conclusions

- PD biomarker qualification
  - Robust and scientifically sound assays
  - Analytical validation (Accuracy, Precision - repeatability, reproducibility) – **Good science**
- PD biomarkers provide critical information about
  - Drug efficacy
  - Optimal dose
  - Safety and mechanisms of action
- Good biomarkers are excellent value for money and should be a key component of every Phase I/II study

Biomarker obstacles

- Additional time for development, validation
- Increased costs (although should be relatively modest)
- Different assays for each class of the drugs
- Technically challenging – experienced and creative scientists
- Expert laboratory (where to find them)?
  - CRO
  - Pharmaceutical industry
  - Academy

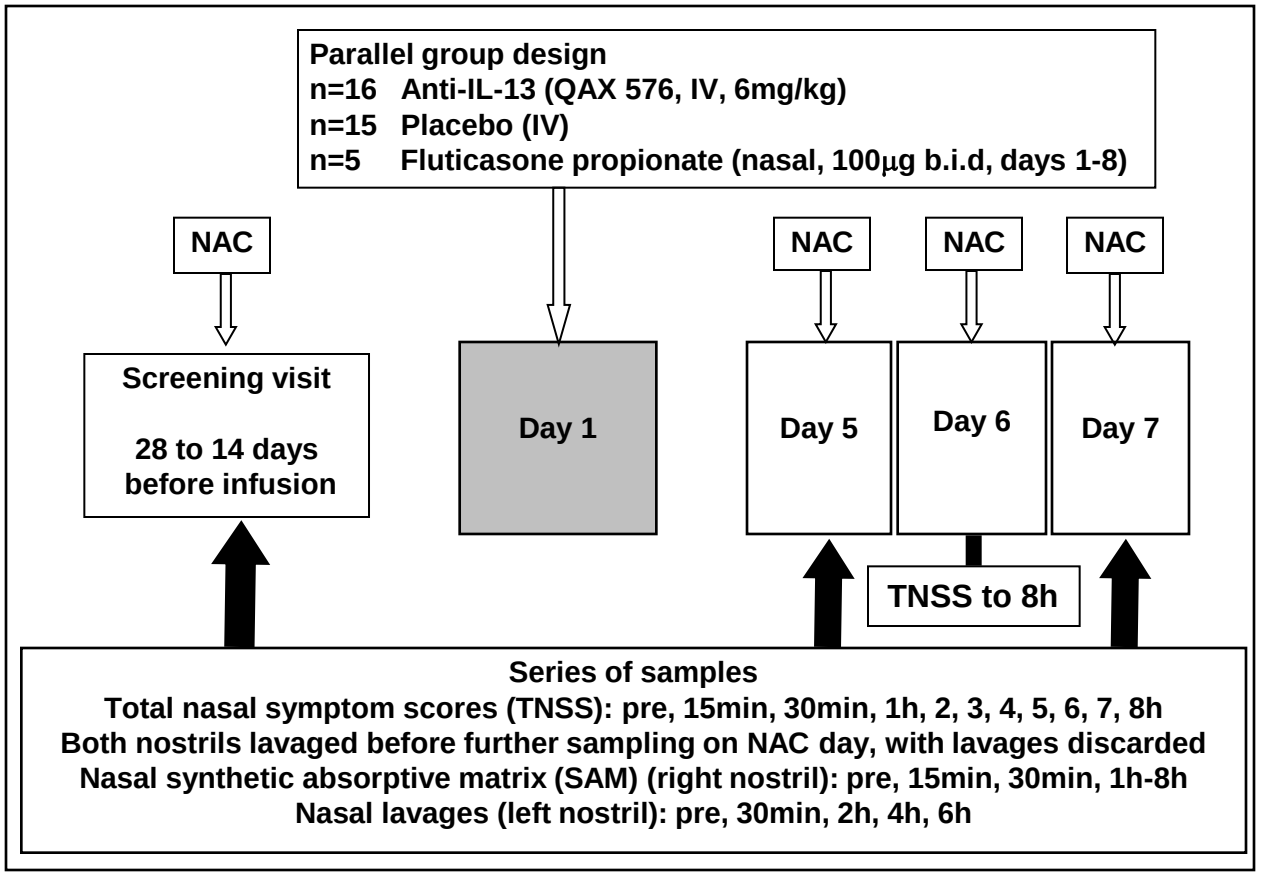
Biomarker solutions

- Small, flexible, inexpensive (base costs, overheads) expert laboratories
- Academia
  - Huge capacity, wide expertise
  - Modest base costs (experts and equipment are already there)
  - Good science (peer reviewed publication - similar to validation)
- Collaboration (Industry - Academia)
  - Competitive edge via access to best scientists/labs
  - Improved quality of clinical trials
  - More published trials – knowledge base
- Establish workable principles for collaboration?
- Role of Human Pharmacology Societies?

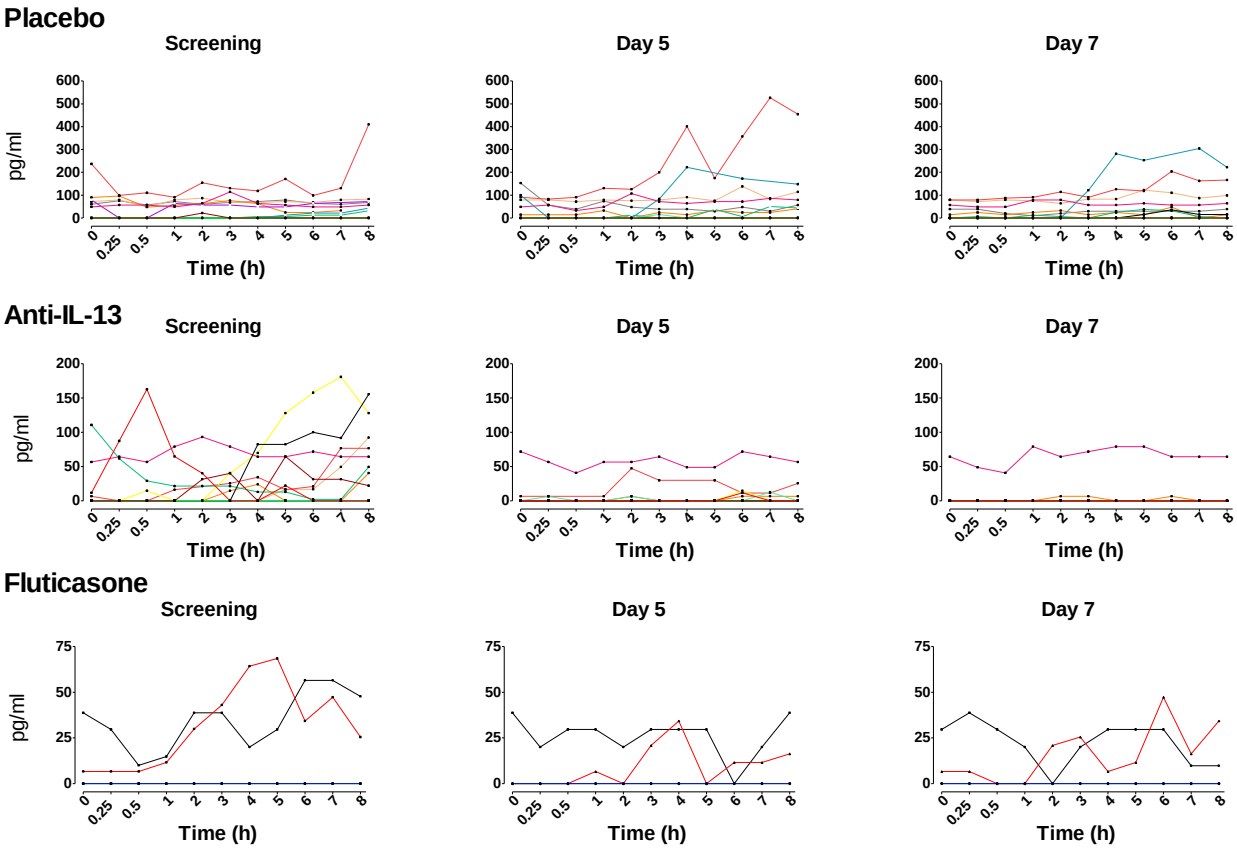
Nasal allergen challenge study – biomarkers and patient sub-groups

- Patients with seasonal grass pollen allergic rhinitis (a model for allergic reaction & possibly for asthma)
- Measurement of mediators of inflammation (PGD2, tryptase), cytokines, chemokines, etc
- Total nasal symptom scores (TNSS)
- Eosinophil levels in nasal lavage
- Anti-IL-13 mAb effects on TNSS, eosinophils and cytokine levels
- open label group receiving topical nasal corticosteroid fluticasone (n=5)

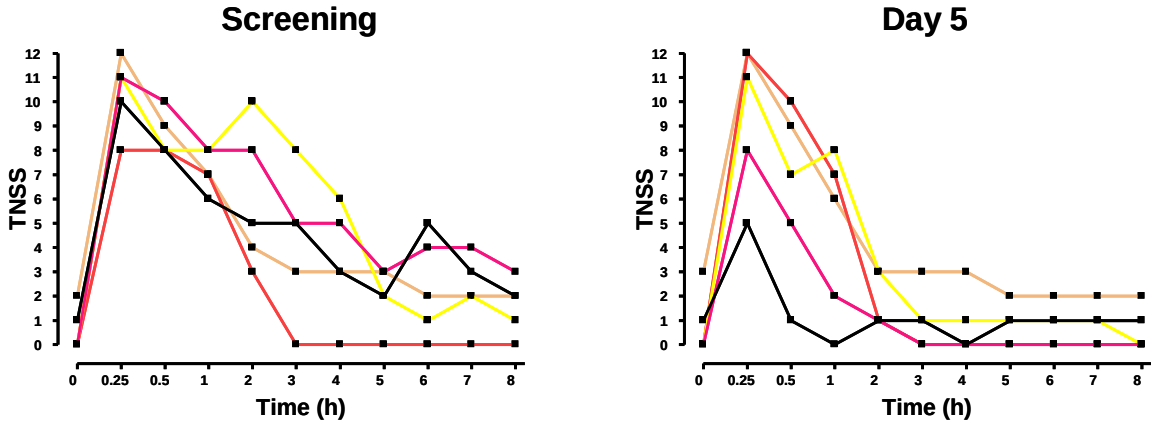
NAC study design



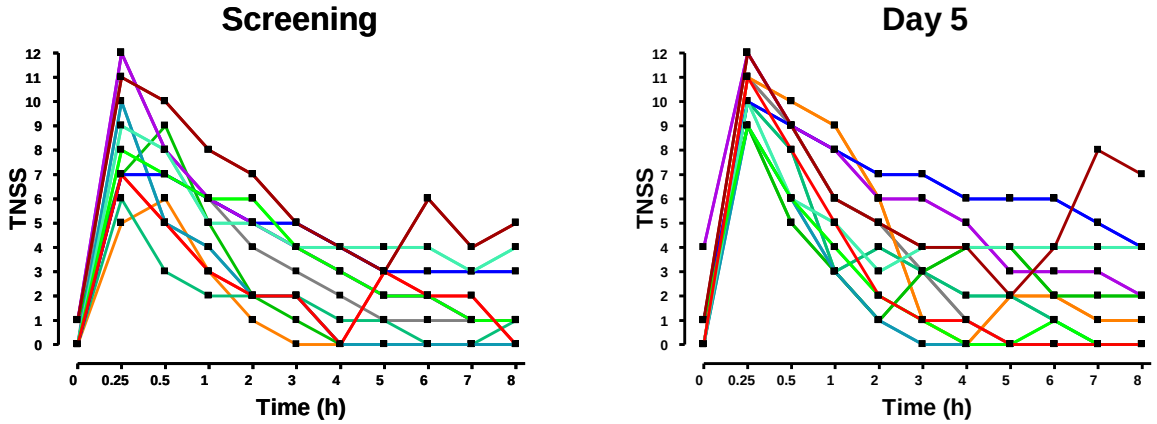
IL-13 levels in placebo, anti-IL-13 and Fluticasone groups



TNSS in Subjects with High Interleukin-13 levels



TNSS in Subjects with Low Interleukin-13 levels

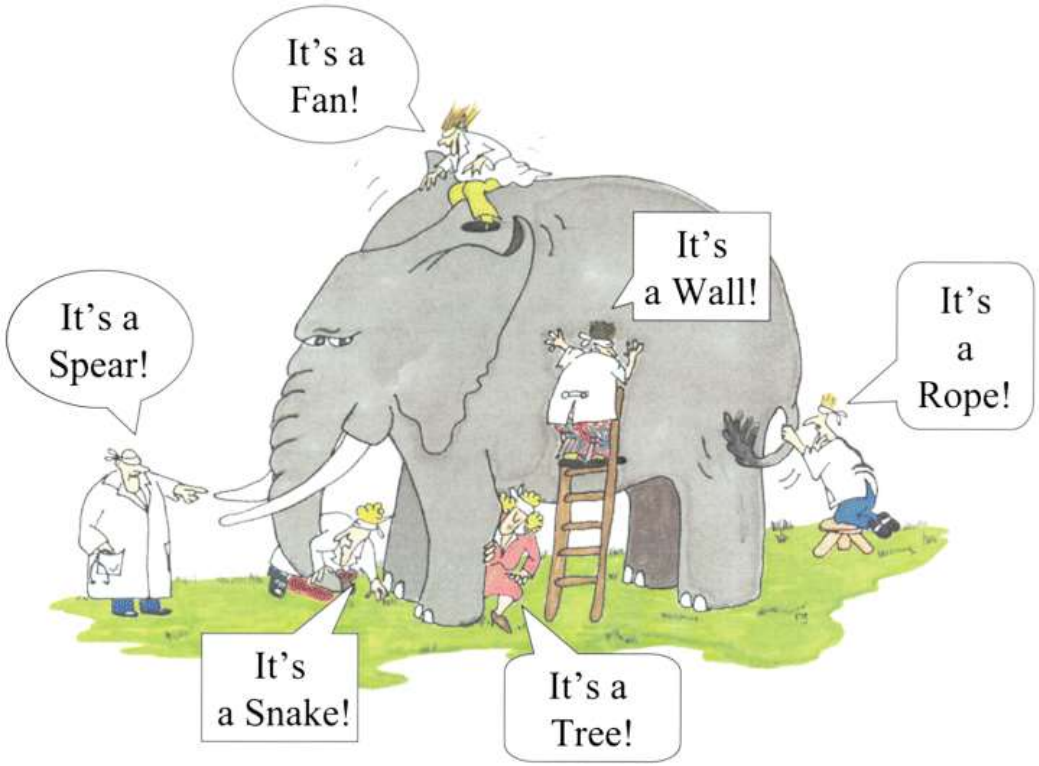


Total nasal symptom scores (TNSS) from the cohort receiving anti-IL-13 treatment. Subjects have been separated into high IL-13 and low IL-13 groups based on IL-13 measurement from SAM eluates at 7h and 8h after NAC at screening

Biomarkers for patient sub-populations

- Possible effect on nasal symptoms in a subgroup of patients with high IL-13 levels in the late phase after screening NAC.
- Similarly, anti–IL-5 is effective in preventing eosinophilic exacerbations of asthma when given to selected patients with severe eosinophilic asthma

Acknowledgements



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